JUDGE CARTER

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

12 CIV 8115

ENDO PHARMACEUTICALS INC, and GRÜNENTHAL GMBH,

Plaintiffs,

v.

AMNEAL PHARMACEUTICALS, LLC and AMNEAL PHARMACEUTICALS OF NEW YORK, LLC,

Defendants.

C.A. No. ____________

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COMPLAINT

Plaintiff Endo Pharmaceuticals Inc. ("Endo") for its Complaint against Defendants Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals of New York, LLC (collectively, "Amneal"), alleges as follows:

PARTIES

1. Plaintiff Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317. Endo is a specialty Pharmaceuticals company engaged in the research, development, sale and marketing of prescription pharmaceuticals used, among other things, to treat and manage pain. Endo markets and distributes OPANA® ER, an innovative crush-resistant opioid (alternatively referred to herein as "Opana ER CRF").

2. Plaintiff Grünenthal GmbH ("Grünenthal") is a corporation organized and existing under the laws of Germany, having an address at 52078 Aachen, Zieglerstaβe 6, North Rhine-Westaphalia, Germany. Endo has joined Grünenthal as a plaintiff in this matter by virtue

of its status as owner of certain of the patents-in-suit, as described in more detail below, and Grünenthal joins this matter as a plaintiff solely for prudential jurisdiction purposes.

3. Upon information and belief, Amneal Pharmaceuticals, LLC ("Amneal Pharmaceuticals") is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 440 U.S. Highway 22 East, Suite 104, Bridgewater, NJ 08897.

4. Upon information and belief, Amneal Pharmaceuticals is a pharmaceutical company engaged in the research, development, production, distribution, and sale of generic pharmaceuticals throughout the United States, including sales within this judicial district.

5. Upon information and belief, Amneal Pharmaceuticals of New York, LLC ("Amneal New York") is a limited liability company organized and existing under the laws of the State of Delaware, and shares a principal place of business with Amneal Pharmaceuticals' administrative offices at 85 Adams Avenue, Hauppauge, New York 11788.

6. Upon information and belief, Amneal New York is a pharmaceutical company engaged in the manufacturing for and the sale of generic prescription pharmaceutical products to Amneal Pharmaceuticals for distribution throughout the United States, including in this judicial district.

NATURE OF ACTION

7. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 100, *et seq*. and the Declaratory Judgment Act, 28 U.S.C. § 2201, *et seq*.

JURISDICTION AND VENUE

8. This Court has jurisdiction over the subject matter of this action pursuant to 28

U.S.C. §§ 1331 and 1338(a) (patent infringement), and 28 U.S.C. §§ 2201 and 2202 (declaratory judgment).

9. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and 1400(b).

10. Upon information and belief, Amneal Pharmaceuticals conducts its North American operations in part through Amneal New York. Together, Amneal Pharmaceuticals and Amneal New York collaborate in the research, development, manufacture, testing, distribution and/or the sale of a number of pharmaceutical products manufactured and sold pursuant to approved abbreviated new drug applications within the United States and the State of New York generally and this judicial district specifically.

11. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, they have committed — or aided, abetted, planned, contributed to, or participated in the commission of — tortious conduct in the State of New York that has led to foreseeable harm and injury to Endo.

12. Upon information and belief, Amneal Pharmaceuticals has submitted to FDA paperwork purporting to constitute an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j) ("ANDA No. 20-4294" or "Amneal's ANDA"), seeking approval to engage in the commercial manufacture, use, and sale of 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg oxymorphone hydrochloride extended-release tablets, ("Amneals's ANDA Products"), as a generic version of the drug described in Endo's sNDA 201655.

13. Upon information and belief, Amneal both manufactures the Amneal ANDA Products and conducts testing necessary to validate their quality in the State of New York. On further information and belief, Amneal intends to manufacture and test Amneal's ANDA

Products produced for commercial sale in the State of New York.

14. Upon information and belief, Amneal New York intends to manufacture generic Opana ER CRF for distribution and sale in this judicial district should Amneal's ANDA be approved by FDA. Upon information and belief, Amneal Pharmaceuticals intends to distribute and sell generic Opana ER CRF in this judicial district should ANDA No. 20-4294 be approved by FDA.

15. Moreover, Amneal Pharmaceuticals and Amneal New York maintain continuous and systematic contacts with the State of New York and this District.

16. Upon information and belief, Amneal Pharmaceuticals and Amneal New York are registered with the New York State Department of State as corporations actively conducting business within New York and maintain a registered agent within the state.

17. Upon information and belief, Amneal Pharmaceuticals currently sells significant quantities of generic drug products in the Southern District of New York. Those products include, for example, generic versions of Percocet®, Ultracet®, and Neurontin®. A list of generic products manufactured and sold by Amneal Pharmaceuticals in the United States can be found at http://www.amneal.com/index.php.

18. Upon information and belief, Amneal Pharmaceuticals maintains an administrative office at 85 Adams Avenue, Hauppauge, NY 11788; an oral solids manufacturing facility at 75 Adams Avenue, Hauppauge, NY 11788; an oral solids and softgels manufacturing facility at 50 Horseblock Road, Brookhaven, NY 11719; and an oral solids research and development facility at 50 Horseblock Road, Brookhaven, NY 11719.

19. Upon information and belief, Amneal New York's principal place of business is located at 85 Adams Avenue, Hauppauge, New York 11788.

20. Furthermore, Amneal Pharmaceuticals has been sued as a patent infringer in this Court, asserted counterclaims in this Court, and declined to contest that this Court has personal jurisdiction over it. *See, e.g.*, *Purdue Pharm, L.P., et al. v. Amneal Pharmaceuticals, LLC*, 11-cv-08153-SHS-JLC; *Pfizer Inc., et al. v. Actavis Inc., et al.*, 10-cv-8197-(TPG).

21. Based on the facts and causes alleged herein, and for additional reasons to be developed through discovery, this Court has personal jurisdiction over the Defendants.

FACTUAL BACKGROUND

The Drug Approval Process

22. A company seeking to market a new drug in the United States must first obtain approval from FDA, typically through the filing of a New Drug Application ("NDA"). *See* 21 U.S.C. § 355(a). The sponsor of the NDA is required to submit information on all patents claiming the drug that is the subject of the NDA, or a method of using that drug, to FDA, and upon approval, FDA then lists such patent information in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the "Orange Book." *See* 21 U.S.C. § 355(b)(1) and (c)(2).

23. On the other hand, a company seeking to market a generic version of a previously approved drug is not required to submit a full NDA. Instead, it may file an ANDA. *See* 21 U.S.C. § 355(j). The generic drug approval process is considered "abbreviated" because the generic manufacturer may piggyback on the innovator company's data and FDA's prior finding of safety and efficacy by demonstrating, among other things, that the generic product is bioequivalent to the previously approved drug (the "listed drug" or "branded drug").

24. In conjunction with this "abbreviated" application process, Congress has put in place a process for resolving patent disputes relating to generic drugs, under which an ANDA

filer must provide certifications addressing each of the patents listed in the Orange Book for the branded drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12). An ANDA filer may certify, for instance, that it believes a patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A)(4). This is known as a "Paragraph IV Certification."

25. The sponsor of an ANDA which is accepted for review by FDA that contains a Paragraph IV Certification must provide notice ("Paragraph IV Notice") to both the owner of the listed patents and the holder of the NDA for the referenced listed drug. The certification must include a detailed statement of the factual and legal bases for the applicant's belief that the challenged patent is invalid or not infringed by the proposed generic product. 21 U.S.C. § 355(j)(2)(B); 21 C.F.R. § 314.95.

26. If the patentee or NDA holder files a patent infringement action within 45 days of receiving a Paragraph IV Notice from an ANDA filer, final approval of the ANDA is generally subject to a 30-month stay of regulatory approval. *See* 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(b)(3). The 30-month stay is important to innovator companies, such as Endo and Grünenthal, because it protects them from the severe financial harm that could otherwise ensue from FDA granting approval to a potentially infringing product without first providing an opportunity for the innovators to prove infringement and obtain an injunction prohibiting sale of the infringing product. Put another way, the innovator company is assured of a 30-month period during which it may try to enforce its intellectual property rights and resolve any patent dispute before the generic product enters the market. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

Endo's Opana ER CRF NDA

27. On December 12, 2011, FDA approved Endo's Supplemental New Drug Application ("sNDA") 201655, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for a new dosage form of Opana ER which is a crush-resistant tablet that contains oxymorphone hydrochloride for the relief of pain (hereinafter, "Opana ER CRF").

28. Opana ER CRF is distributed and sold throughout the United States for relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time.

THE '482 PATENT

29. On December 14, 2010, the PTO duly and legally issued U.S. Patent No. 7,851,482 ("the '482 Patent"), entitled "Method for Making Analgesics" to Johnson Matthey Public Limited Company ("Johnson Matthey") as assignee. Jen-Sen Dung, Erno M. Keskeny, and James J. Mencel are named as inventors. A true and correct copy of the '482 Patent is attached as Exhibit A.

30. Endo subsequently acquired full title to the '482 Patent, and accordingly, Endo is now the sole owner and assignee of the '482 Patent.

31. Information regarding the Endo '482 Patent was submitted to FDA for listing in the Orange Book. Pursuant to 21 C.F.R. § 314.53(e), FDA has listed the '482 Patent in the Orange Book with reference to NDA 201655.

32. Opana ER CRF is covered by one or more claims of the '482 Patent.

THE '722 PATENT

33. On June 5, 2012, the PTO duly and legally issued U.S. Patent No. 8,192,722 ("the '722 Patent"), entitled "Abuse-Proofed Dosage Form" to Gruenenthal GmbH, also known as

Grünenthal GmbH, as assignee. Elisabeth Arkenau-Marić, Johannes Bartholomäus, and Heinrich Kugelmann are named as inventors. A true and correct copy of the '722 Patent is attached as Exhibit B. The '722 Patent expires on September 15, 2025.

34. Grünenthal is the assignee and owner of the '722 Patent.

35. Endo has an exclusive license to the '722 Patent from Grünenthal, including a right to enforce the '722 Patent.

36. Information regarding the '722 Patent was submitted to FDA for listing in the Orange Book. Pursuant to 21 C.F.R. § 314.53(e), FDA has listed the '722 Patent in the Orange Book in reference to NDA 201655.

37. Opana ER CRF is covered by one or more claims of the '722 Patent.

AMNEAL'S ANDA FILING

38. Upon information and belief, some time before September 21, 2012, Amneal submitted to FDA paperwork purporting to constitute an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg oxymorphone hydrochloride extended-release tablets ("Amneal's ANDA Products"), as a generic version of the products described in sNDA 201655.

39. In a letter dated September 21, 2012 addressed to Endo and received on or about September 24, 2012, and in a separate letter addressed to Grünenthal dated October 10, 2012 and received by Grünenthal on or about that same day, Amneal purported to notify Plaintiffs that Amneal had submitted ANDA No. 20-4294, seeking approval to manufacture, use, or sell Amneal's ANDA Products before the expiration of the '482 and '722 Patents ("Amneal Notice Letters").

40. The Amneal Notice Letters claimed that Amneal's ANDA included a Paragraph IV Certification stating that it was Amneal's opinion that the claims of the '482 and '722 Patents are invalid, unenforceable, or are not infringed by the proposed manufacture, importation, use, sale, or offer for sale of the Amneal ANDA Products.

41. This action is being commenced before the expiration of forty-five days from the date Endo and Grünenthal received the Amneal Notice Letters.

COUNT I: INFRINGEMENT OF THE '482 PATENT

42. Endo incorporates each of paragraphs 1-41 above as if set forth fully herein.

43. The submission of Amneal's ANDA to FDA, which includes certification under § 505(j)(2)(A)(vii)(IV), constitutes infringement of the '482 Patent under 35 U.S.C. § 271(e)(2)(A).

44. Amneal is seeking FDA approval to engage in the commercial manufacture, use, or sale of Amneal's ANDA Products before the expiration of the '482 Patent. If granted approval, Amneal intends to launch its ANDA Products before expiration of the '482 Patent.

45. Amneal's commercial manufacture, offer for sale, or sale of its ANDA Products would infringe the '482 Patent under 35 U.S.C. § 271(a)-(c).

46. Any launch by Amneal of its ANDA Products before expiration of the '482 Patent would cause Endo to suffer immediate and irreparable harm.

47. Amneal was aware of the existence of the '482 Patent, as demonstrated by its reference to that patent in the Amneal Notice Letters, and was aware that the filing of its Paragraph IV Certification with respect to the '482 Patent would constitute infringement of the patent.

COUNT II: INFRINGEMENT OF THE '722 PATENT

48. Endo incorporates each of paragraphs 1-41 above as if set forth fully herein.

49. The submission of Amneal's ANDA to FDA, which includes certification under § 505(j)(2)(A)(vii)(IV), constitutes infringement of the '722 Patent under 35 U.S.C. § 271(e)(2)(A).

50. Amneal is seeking FDA approval to engage in the commercial manufacture, use, or sale of its ANDA Products before the expiration of the '722 Patent. If granted approval, Amneal intends to launch Amneal's ANDA Products before expiration of the '722 Patent.

51. Amneal's commercial manufacture, offer for sale, or sale of its ANDA Products would infringe the '722 Patent under 35 U.S.C. § 271(a)-(c).

52. Any launch by Amneal of its ANDA Products before expiration of the '722 Patent would cause Endo to suffer immediate and irreparable harm.

53. Amneal was aware of the existence of the '722 Patent, as demonstrated by its reference to that patent in the Amneal Notice Letters, and was aware that the filing of its Paragraph IV Certification with respect to the '722 Patent would constitute infringement of the patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Endo respectfully requests the following relief:

A. A judgment that Defendants have infringed the '482 Patent, and a declaration that Amneal's commercial manufacture, distribution, use, and sale of its ANDA Products would infringe the '482 Patent;

B. A declaration that the '482 Patent is valid and enforceable;

C. A judgment that Amneal has infringed the '722 Patent, and a declaration that

Amneal's commercial manufacture, distribution, use, and sale of its ANDA Products would infringe the '722 Patent;

D. A declaration that the '722 Patent is valid and enforceable;

E. An order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any approval of Amneal's ANDA No. 20-4324 under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), shall not be earlier than the last expiration date of the '482 and '722 Patents, including any extensions;

F. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Amneal, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringement of the '482 and '722 Patents for the full terms thereof, including any extensions;

G. An order that damages or other monetary relief be awarded to Endo if Amneal engages in the commercial manufacture, use, offer to sell, sale, distribution or importation of Amneal's ANDA Products, or in inducing such conduct by others, prior to the expiration of the '482 and '722 Patents, and any additional period of exclusivity to which Plaintiffs are or become entitled, and that any such damages or monetary relief be trebled and awarded to Endo with prejudgment interest;

H. A declaration that this an exceptional case and an award of reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

I. Reasonable attorneys' fees, filing fees, and reasonable costs of suit incurred by Endo and Grünenthal in this action; and

J. Such other and further relief as the Court may deem just and proper.

Dated: November 7, 2012

By:____________________________

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Exhibit A

US007851482B2

(12) **United States Patent**
Dung et al.

(10) **Patent No.: US 7,851,482 B2**
(45) **Date of Patent: Dec. 14, 2010**

(54) **METHOD FOR MAKING ANALGESICS**

(75) Inventors: **Jen-Sen Dung**, Boothwyn, PA (US); **Erno M. Keskeny**, Wilmington, DE (US); **James J. Mencel**, North Wales, PA (US)

(73) Assignee: **Johnson Matthey Public Limited Compnay**, London (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 646 days.

(21) Appl. No.: **11/866,840**

(22) Filed: **Oct. 3, 2007**

(65) **Prior Publication Data**

US 2008/0146601 A1 Jun. 19, 2008

(30) **Foreign Application Priority Data**

Dec. 14, 2006 (GB) 0624880.1

(51) **Int. Cl.**
A61K 31/485 (2006.01)
C07D 489/04 (2006.01)

(52) **U.S. Cl.** **514/282**; 546/45; 546/44

(58) **Field of Classification Search** 514/282; 546/45, 44
See application file for complete search history.

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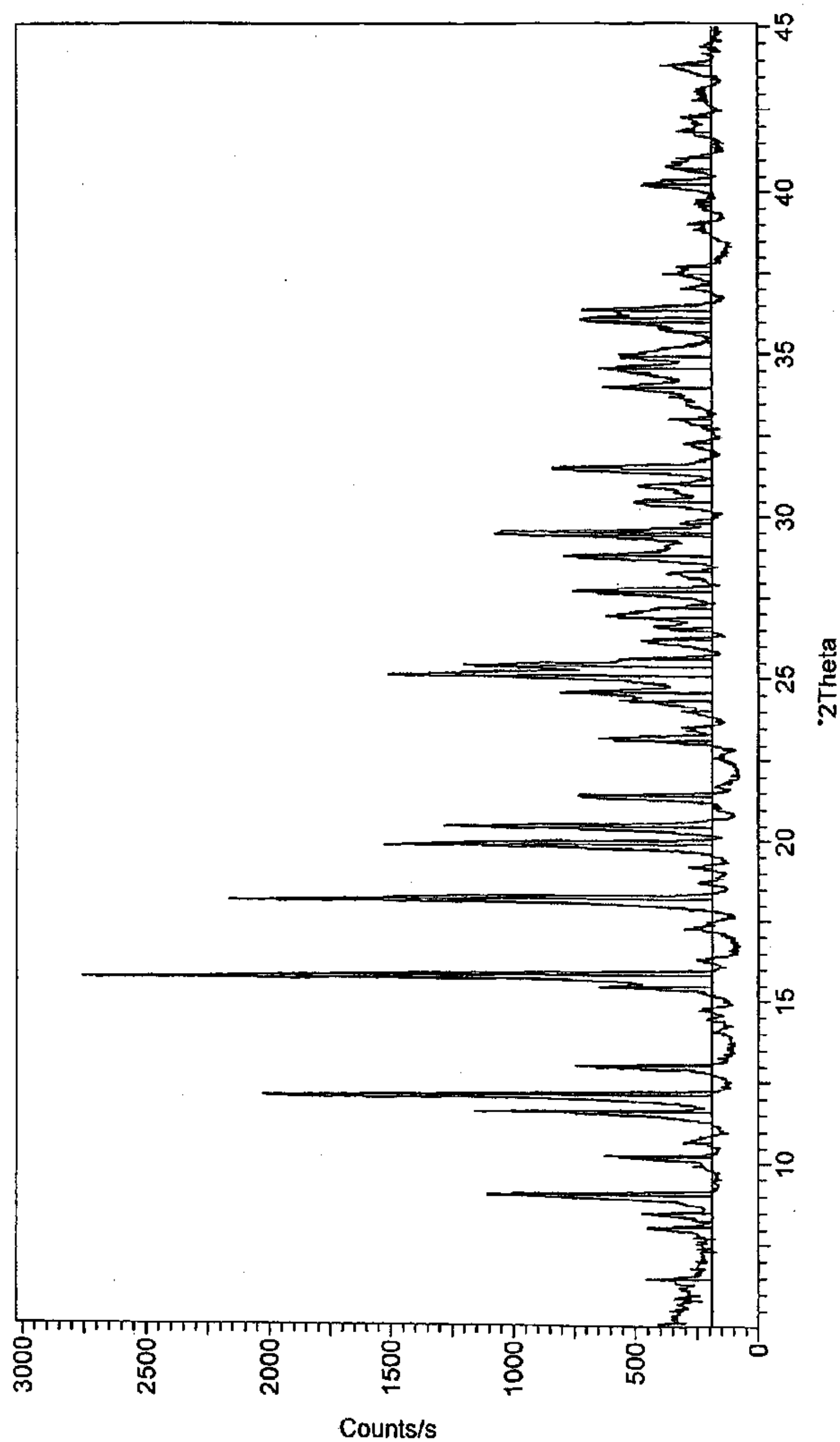
Primary Examiner—Charanjit S Aulakh
(74) *Attorney, Agent, or Firm*—RatnerPrestia

(57) **ABSTRACT**

Improved analgesic oxymorphone hydrochloride contains less than 10 ppm of alpha, beta unsaturated ketones and pharmaceutical preparations comprising such oxymorphone hydrochloride. The oxymorphone hydrochloride is produced by reducing a starting material oxymorphone hydrochloride using gaseous hydrogen and under specified acidity, solvent system and temperature conditions. A specific polymorph of oxymorphone hydrochloride may be obtained by hydration.

21 Claims, 1 Drawing Sheet



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METHOD FOR MAKING ANALGESICS

FIELD OF THE INVENTION

This invention concerns an improved method for making analgesics, more especially for making the opiate oxymorphone as its hydrochloride.

BACKGROUND OF THE INVENTION

Oxymorphone, generally administered in the form of its hydrochloride salt, is a potent semi-synthetic opiate analgesic, for the relief of moderate to severe pain, and has been approved for use since 1959. It can be administered as an injectable solution, suppository, tablet or extended release tablet. It is desirable to develop high purity forms of oxymorphone and a method for its synthesis.

Several methods for synthesising oxymorphone from compounds isolated from the opium poppy or compounds derived therefrom are known, for example, starting from morphine, thebaine, or from oxycodone. There remains the need for methods which permit the formation of oxymorphone with low contamination of alpha, beta unsaturated ketones. The present invention provides an improved oxymorphone product and a method for producing such oxymorphone.

U.S. Pat. No. 7,129,248 claims a process for producing oxycodone hydrochloride with less than 25 ppm of 14-hydroxycodeinone, by hydrogenating oxycodone having greater than 100 ppm 14-hydroxycodeinone. The synthetic route to oxycodone taught in US'248 starts from thebaine and produces 14-hydroxycodeinone as an intermediate product and 8,14-dihydroxy-7,8-dihydrocodeinone as a by-product resulting from over-oxidation of thebaine. During conversion of oxycodone free base to the hydrogen chloride salt, the by-product may undergo acid-catalysed dehydration and be converted into 14-hydroxycodeinone. Thus the final oxycodone hydrogen chloride salt contains unreacted 14-hydroxycodeinone as well as 14-hydroxycodeinone derived from the by-product 8,14-dihydroxy-7,8-dihydrocodeinone. A hydrogenation step is claimed to reduce contents of 14-hydroxycodeinone from at least 100 ppm to less than 25 ppm.

SUMMARY OF THE INVENTION

The present invention provides an oxymorphone hydrochloride product containing less than 10 ppm of alpha, beta unsaturated ketones.

The invention also provides a method of purifying oxymorphone hydrochloride to yield an oxymorphone hydrochloride product containing less than 10 ppm of alpha, beta unsaturated ketones, which method comprises reducing a starting material oxymorphone hydrochloride in a strongly acid water and alcohol solvent, using gaseous hydrogen at a temperature in the range from 60 to 70° C. Reduction is suitably carried out for a period of at least 20 hours, but in another embodiment, reduction is carried out for 1 to 20 hours.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described below with reference to the drawing, in which:

FIG. 1 is the Powder X-Ray Diffraction pattern collected for a hydrated oxymorphone hydrochloride product made according to Example 3.2D.

DETAILED DESCRIPTION OF THE INVENTION

Preferably, the solvent is ethanol/water, although other water miscible alcohols, such as isopropanol and n-propanol, may be used. The reaction medium is very acidic, preferably by incorporating at least two equivalents of hydrochloric acid. A pH of less than 1 is desirable.

The reaction temperature is most preferably maintained at about 65° C. Hydrogen is conveniently supplied to the reaction vessel at 2.41 bar pressure.

The method of the invention has been able to reduce starting material oxymorphone hydrochloride having very high (of the order of 0.3 to 0.5%, or 3,000 to 5,000 ppm) content of alpha, beta unsaturated ketones to less than 10 ppm, and in many cases to undetectable levels (by HPLC).

The starting material oxymorphone hydrochloride may be an isolated or non-isolated material. Desirably, it has been obtained by the formation of the hydrogen chloride salt by heating oxymorphone free base in the presence of hydrochloric acid and an alcohol/water reaction medium. Suitable temperatures are 60-70° C. It can be seen that the reaction medium is ideal for the reduction of the method of the invention, so that it is generally not necessary to isolate the oxymorphone hydrochloride. However, the starting material oxymorphone hydrochloride may be isolated from the reaction medium or may be from another source.

The oxymorphone free base is itself preferably prepared by a reduction of 14-hydroxymorphinone. This may be carried out in a single- or two-stage process. The reduction is preferably carried out in acetic acid using gaseous hydrogen and a palladium on carbon catalyst. Preferred temperatures are of the order of 30° C. The base is precipitated by adding aqueous ammonia (NH_4OH).

This reduction may be in the presence of the reaction medium to which is added dichloromethane in methanol, Florasil and n-propanol.

The 14-hydroxymorphinone itself is most suitably prepared by hydroxylation of oripavine, using hydrogen peroxide in the presence of formic acid.

Oripavine is a known compound, which is extractable from poppy straw. The strain developed in Tasmania to be a high-Thebaine-yielding strain also produces higher than normal levels of oripavine.

The process of the invention is highly flexible, permitting many reaction steps to be carried out without isolation of intermediate products, whilst still retaining high (of the order of 50%) overall yields from oripavine, as well as remarkably high purity. Under favourable conditions, the presence of alpha, beta unsaturated ketones is undetectable by conventional means such as HPLC, but the skilled person can readily achieve less than 10 ppm contamination. The process of the invention has been successfully carried out at kilogram scale.

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be incorporated into pharmaceutical dosage forms, e.g., by admixtures of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances. For oral formulations, the dosage forms can provide a sustained release of the active component. Suitable pharmaceutically acceptable carriers include but are not limited to, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy-methylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, disintegrants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, colouring, flavouring and/or aro-

matic substances and the like. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent. The oral dosage forms of the present invention may be in the form of tablets (sustained release and/or immediate release), troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, solutions, suspensions, etc.

In certain embodiments, the present invention provides for a method of treating pain by administering to a human patient the dosage forms described herein.

When the dosage form is oral, the dosage form of the present invention contains from about 1 mg to about 40 mg of oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. Particularly preferred dosages are about 5 mg, about 10 mg, about 20 mg or about 40 mg however other dosages may be used as well. The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can also be formulated with suitable pharmaceutically acceptable excipients to provide a sustained release of having less than 10 ppm of alpha, beta unsaturated ketones. Such formulations can be prepared in accordance with US 2003/129230 A1, US 2003/129234 A1 and US 2003/157167 A1.

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be formulated as a sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may include a sustained release material that is incorporated into a matrix along with the oxymorphone salt thereof.

The sustained release dosage form may optionally comprise particles containing oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. In certain embodiments, the particles have a diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Preferably, the particles are film coated with a material that permits release of the active at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, desired release properties. The sustained release coating formulations of the present invention should preferably be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Coated Beads

In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, and a plurality of the resultant solid sustained release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

The sustained release bead formulations of the present invention slowly release the active component of the present invention, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticiser is added to the hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with the agent(s) of the present are prepared, e.g., by dissolving the agent(s) in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the active to the beads, and/or to color the solution, etc. For example, a product that includes hydroxypropylmethylcellulose, etc with or without colorant (e.g., Opadry™, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in these example beads, may then be optionally overcoated with a barrier agent, to separate the active component(s) from the hydrophobic sustained release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticiser, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat™ or Surelease™, may be used. If Surelease™ is used, it is not necessary to separately add a plasticiser. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit™ can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticiser, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Colour may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, colour may be added to Aquacoat™ via the use of alcohol or propylene glycol based colour dispersions, milled aluminium lakes and opacifiers such as titanium dioxide by adding colour with shear to water soluble polymer solution and then using low shear to the plasticised Aquacoat™. Alternatively, any suitable method of providing colour to the formulations of the present invention may be used. Suitable ingredients for providing colour to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and colour pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

Plasticised hydrophobic material may be applied onto the substrate comprising the agent(s) by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidised-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined sustained release of the agent(s) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, may be applied. After coating with the hydrophobic

material, a further overcoat of a film-former, such as Opadry™, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the agent(s) from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents, which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in an environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,063,064 and U.S. Pat. No. 4,088,864.

Matrix Formulations

In other embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a sustained release coating as set forth herein. The materials suitable for inclusion in a sustained release matrix may depend on the method used to form the matrix.

For example, a matrix in addition to the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones may include: hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials. The list is not meant to be exclusive, any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting sustained release of the agent(s) and which melts (or softens to the extent necessary to be extruded) may be used in accordance with the present invention.

Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols. Of these polymers, acrylic polymers, especially Eudragit™. RSPO—the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25° C. and 90° C. Of the long chain hydrocarbon materials, fatty

(aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, the oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol.

The hydrophobic material is preferably selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly (methacrylic acid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 25° C. to about 200° C., preferably from about 45° C. to about 90° C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For the purposes of the present invention, a wax-like substance is defined as any material that is normally solid at room temperature and has a melting point of from about 25° C. to about 100° C.

Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25° C. and 90° C. are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon. Preferably, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropyl-methylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxymorphone hydrochloride release required. The at least

one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of opioidoxycmorphone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a (w/w) of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, preferably, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000 especially between 1,500 and 12,000.

Another suitable sustained release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials.

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

Matrix—Particulates

In order to facilitate the preparation of a solid, sustained release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose, and the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12} to C_{36} aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxalkyl cellulose granules with water.

In yet other alternative embodiments, a spheronizing agent, together with the active component can be spheronized to form spheroids. Microcrystalline cellulose is a preferred spheronizing agent. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropyl-cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Melt Extrusion Matrix

Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Pat. No. 4,861,598.

The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

Melt Extrusion Multiparticulates

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 mm to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 hours to about 24 hours.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, the oxymorphone hydrochloride

having less than 10 ppm of alpha, beta unsaturated ketones, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For the purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 mm to about 12 mm in length and have a diameter of from about 0.1 mm to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tabletting equipment using standard techniques. Techniques and compositions for making tablets (compressed and moulded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681, described in additional detail above.

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule containing the multiparticulates can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2% to about 30%, although the overcoat may be greater depending upon the desired release rate, among other things.

The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded particles before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release agent for prompt release. The immediate release agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., sustained release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of sustained release beads and matrix multiparticulates to achieve a desired effect.

The sustained release formulations of the present invention preferably slowly release the agent(s), e.g. when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones, which can be added thereafter to the extrudate. Such formulations typically will have the agents blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation.

Coatings

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release. A pH-dependent coating serves to release the active in desired areas of the gastrointestinal (GI) tract, e.g. the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions that release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones thereof is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2% to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described in detail U.S. Pat. No. 5,273,760, U.S. Pat. No. 5,286,493, U.S. Pat. No. 5,324,351, U.S. Pat. No. 5,356,467, and U.S. Pat. No. 5,472,712.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose,

although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

Acrylic Polymers

In other preferred embodiments of the present invention, the hydrophobic material comprising the sustained release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described as fully polymerised copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings, which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit™ from Rohm Tech, Inc. There are several different types of Eudragit™, for example Eudragit™ E is an example of a methacrylic acid copolymer that swells and dissolves in acidic media. Eudragit™ L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit™ S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit™ RL and Eudragit™ RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit™ RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit™ RL30D and Eudragit™ RS30D, respectively. Eudragit™ RL30D and Eudragit™ RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit™ RL30D and 1:40 in Eudragit™ RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit™ RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit™ RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit™ RL, 50% Eudragit™ RL and 50% Eudragit™ RS, or 10% Eudragit™ RL and 90% Eudragit™ RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit™ L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticiser in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethyl-cellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticiser into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticiser included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 wt % to about 50 wt % of the film-former. Concentration of the plasticiser, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers that have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit™ RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

The addition of a small amount of talc may also help reduce the tendency of the aqueous dispersion to stick during processing, and may act as a polishing agent.

Sustained Release Osmotic Dosage Form

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones) and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be pumped, diffuse or migrate through a fibre, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be

formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,063,064 and U.S. Pat. No. 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in U.S. Pat. No. 4,200,098 and U.S. Pat. No. 4,285,987.

In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_n H_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethyl-cellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as an osmogel), whereby they push the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones thereof from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulphate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulphate, sodium sulphate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkyl-cellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer optionally may comprise a non-toxic colorant or dye. Examples of colourants or dyes include but are not limited to Food and Drug Administration Colourants (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide, carbon black, and indigo.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydrogaaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a homogenous core comprising oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation, semipermeable crosslinked polystyrenes, semipermeable crosslinked poly(sodium styrene sulfonate), semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride) and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} (cm^2/hr atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present

invention are known in the art including those in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

In certain preferred embodiments, the present invention includes a therapeutic composition comprising an amount of oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones equivalent to 10 to 40 mg oxymorphone hydrochloride, 25 mg to 500 mg of poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 mg to 50 mg of polyvinylpyrrolidone having a 40,000 average molecular weight, and 0 mg to about 7.5 mg of a lubricant.

Suppositories

The sustained release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising a suitable suppository base, and oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. Preparation of sustained release suppository formulations is described in, e.g., U.S. Pat. No. 5,215,758.

Prior to absorption, the drug must be in solution. In the case of suppositories, solution must be preceded by dissolution of the suppository base, or the melting of the base and subsequent partition of the drug from the suppository base into the rectal fluid. The absorption of the drug into the body may be altered by the suppository base. Thus, the particular suppository base to be used in conjunction with a particular drug must be chosen giving consideration to the physical properties of the drug. For example, lipid-soluble drugs will not partition readily into the rectal fluid, but drugs that are only slightly soluble in the lipid base will partition readily into the rectal fluid.

Among the different factors affecting the dissolution time (or release rate) of the drugs are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Generally, factors affecting the absorption of drugs from suppositories administered rectally include suppository vehicle, absorption site pH, drug pKa, degree of ionisation, and lipid solubility.

The suppository base chosen should be compatible with the active of the present invention. Further, the suppository base is preferably non-toxic and non-irritating to mucous membranes, melts or dissolves in rectal fluids, and is stable during storage.

In certain preferred embodiments of the present invention for both water-soluble and water-insoluble drugs, the suppository base comprises a fatty acid wax selected from the group consisting of mono-, di- and triglycerides of saturated, natural fatty acids of the chain length C_{12} to C_{18}.

In preparing the suppositories of the present invention other excipients may be used. For example, a wax may be used to form the proper shape for administration via the rectal route. This system can also be used without wax, but with the addition of diluent filled in a gelatin capsule for both rectal and oral administration.

Examples of suitable commercially available mono-, di- and triglycerides include saturated natural fatty acids of the 12-18 carbon atom chain sold under the trade name Novata™ (types AB, AB, B, BC, BD, BBC, E, BCF, C, D and 299), manufactured by Henkel, and Witepsol™ (types H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 and E85), manufactured by Dynamit Nobel.

Other pharmaceutically acceptable suppository bases may be substituted in whole or in part for the above-mentioned mono-, di- and triglycerides. The amount of base in the suppository is determined by the size (i.e. actual weight) of the dosage form, the amount of base (e.g., alginate) and drug used. Generally, the amount of suppository base is from about 20% to about 90% by weight of the total weight of the suppository. Preferably, the amount of suppository base in the suppository is from about 65% to about 80%, by weight of the total weight of the suppository.

Additional Embodiments

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones may be used as a substitute for the oxymorphone hydrochloride in any existing commercial product such as, e.g., Opana™, Opana ER™ and Numorphan™. Such formulations are listed in the FDA Orange Book.

EXAMPLES

The invention will now be illustrated by the following examples, showing the synthesis of the high purity oxymorphone, starting from oripavine.

FIG. 1 is the Powder X-Ray Diffraction pattern collected for a hydrated oxymorphone hydrochloride product made according to Example 3.2D.

Example 1.1A

Hydroxylation of Oripavine to 14-hydroxymorphinone

1 kg oripavine is added with stirring to a reaction vessel containing 2.76 kg of formic acid and 0.53 kg water, and stirring is continued until the oripavine is completely dissolved, and the temperature remains in the range 20-30° C. Subsequently, 0.36 kg of 35 wt % hydrogen peroxide solution

is added, and the reaction mixture is stirred for three hours or more, whilst maintaining the temperature in the range 20-35° C. The reaction vessel is cooled to 10° C. and 7.12 litres of dilute ammonium hydroxide is added slowly, whilst maintaining the reaction mixture below 40° C. If necessary, the pH of the reaction mixture is adjusted to the range 8 to 10, with more dilute ammonium hydroxide solution or hydrochloric acid as appropriate, and stirring is continued for 3-5 hours.

A precipitate of product 14-hydroxymorphinone is formed and filtered off. The precipitate is washed with water until colourless and then dried to a damp cake and collected for the next stage.

Example 1.1B

Formation of Oxymorphone Base

A hydrogenation vessel is charged with kg litre water and 0.73 kg acetic acid before adding 1 kg of 14-hydroxymorphinone prepared as in Example 1.1A and the mixture stirred until clear. 40 g of wet 10% Pd on carbon catalyst is added under a stream of nitrogen, and hydrogen supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 3-4 hours. The reaction vessel is cooled to less than 25° C. and a sample subjected to HPLC to check for 14-hydroxymorphinone. If the 14-hydroxymorphinone area detected by HPLC is >0.1%, the hydrogenation is repeated.

Once it is assessed that the reaction is complete, the catalyst is filtered off, the pH of the filtrate is adjusted to pH 9 using ammonium hydroxide solution, the product precipitates and is isolated by filtration and dried under vacuum. The product is dissolved in dichloromethane/methanol (9:1 v/v) and slurried in florisil, filtered, and the filtrate is distilled to exchange to n-propanol. The n-propanol mixture is cooled and the product precipitates and is collected by filtration in 66% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.51% by area measurement.

Example 1.1C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 1 kg of oxymorphone base, prepared as in Example 1.1B, together with 2.05 kg of absolute alcohol and 0.66 kg of water. The mixture is heated to 60±2° C. and stirred to form a slurry. A hydrochloric acid solution prepared from 0.66 kg concentrated hydrochloric acid, 0.24 kg of water and 0.31 kg of absolute alcohol is added to the oxymorphone base slurry and the pH checked to ensure that it is <1.0. 40 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through Celite and a 0.2 μm polish filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is washed with absolute alcohol then dried. Yield is 80%.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 6.2 ppm.

Example 1.2A

Hydroxylation of Oripavine to 14-hydroxymorphinone

40 g of Oripavine is added with stirring to a reaction vessel containing 30 g of water and 85 g of formic acid, and stirring continued until oripavine is completely dissolved. The temperature remains in the range 20-30° C. Subsequently, 17.72 g of 30 wt % hydrogen peroxide solution is added, and the reaction mixture is stirred for three hours or more, whilst maintaining the temperature in the range 20-35° C. The reaction mixture is cooled to <20° C. and 335 mL of dilute ammonium hydroxide is added slowly, whilst maintaining the reaction mixture below 32° C. If necessary, the pH of the reaction mixture is adjusted to 9.0, with more dilute ammonium hydroxide solution or hydrochloric acid as appropriate, and stirring is continued for 2 hours at 20C and 2 hours at 4-5° C.

A precipitate of 14-hydroxymorphinone is formed and filtered off. The precipitate is washed with water and then dried to a damp cake and collected for the next stage.

Example 1.2B

Formation of Oxymorphone Base

A hydrogenation vessel is charged with 148 g of water, 90.6 g of acetic acid, and 250 g of damp 14-hydroxymorphinone (48% water content), prepared as in Example 1.2A. The mixture is stirred until clear then 1.34 g of 10% Pd on carbon catalyst (dry weight) in the form of a paste is added under a stream of nitrogen. The hydrogenation vessel is flushed with nitrogen and hydrogen respectively, and then the reaction mixture is hydrogenated at 30° C. and 35 psi (2.41 bar) for 5 hours. An in process test by HPLC indicates an 14-hydroxymorphinone area of 0.07%.

Once it is assessed that the reaction is complete, the catalyst is filtered off through a pad of celite, and the celite cake is washed with 25 mL water. The filtrate is cooled to 0-5° C. and the pH is adjusted to 9.5±0.5 with 1:1 mixture (V/V) of concentrated ammonium hydroxide and water. The precipitate is stirred at 0-5° C. for one hour and isolated by filtration. The crude product is dried in vacuum oven at 50° C. to afford 113 g (86.9% yield) of light beige solid. A sample of product is tested by HPLC for alpha, beta unsaturated ketone, and is found to contain 0.27% by area measurement.

113 g of crude oxymorphone base is taken up in 1.13 L of dichloromethane/methanol (9:1, v/v). 113 g of florisil is added to the solution and the mixture is stirred for 12 hours. The mixture is filtered through a pad of 113 g of florisil, and the florisil cake is rinsed with 120 mL of dichloromethane/methanol. The solvent is removed by distillation and then switched to n-propanol. The batch is cooled to 0-5° C. and stirred for 1 hour to precipitate the oxymorphone base, which is filtered off, washed with cold n-propanol, and dried in a vacuum oven to afford 67.2 g (59.47%) of white solids.

A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.027% by area measurement.

Example 1.2C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 50.1 g of oxymorphone base, prepared as in Example 1.2B, together with 120 g of absolute alcohol. The mixture is heated to 60±2° C. and stirred to form a slurry. A hydrochloric acid solution prepared from 32.7 g concentrated hydrochloric acid and 33.6 g of water is added to the oxymorphone base slurry and the pH is checked to ensure that it is <1.0. 2.0 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65° C. The reaction mixture is filtered whilst hot through Celite. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is filtered off, washed with absolute alcohol and then dried to afford white crystals in 77% yield.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 1.1 ppm.

The above method may be varied by the skilled person whilst still maintaining excellent purity of the product oxymorphone hydrochloride, and examples of such variations follow.

Example 2.1B

Reduction of 14-hydroxymorphinone to Oxymorphone Base

A hydrogenation vessel is charged with 2.5 kg of water and 0.73 kg of acetic acid and 1 kg of 14-hydroxymorphinone is added to the vessel. The reaction mixture is stirred until a clear solution is obtained before 40 g of wet 10% Pd on carbon catalyst is added under a stream of nitrogen. Hydrogen is supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 3-4 hours. The reaction vessel is cooled to less than 25° C. and a sample subjected to HPLC to check for 14-hydroxymorphinone. If the 14-hydroxymorphinone area detected by HPLC is >0.1%, the hydrogenation is repeated.

Once it is assessed that the reaction is complete, the catalyst is filtered off, dichloromethane/methanol (9:1 v/v) is added to the filtrate and the mixture is adjusted to pH 9-10 by adding ammonium hydroxide solution. The dichloromethane/methanol phase is separate, slurried in florisil, filtered, and the filtrate is distilled to exchange to n-propanol. The n-propanol mixture is cooled and the product precipitates and is collected by filtration in 73% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.32% by area.

Example 2.2B

Reduction of 14-hydroxymorphinone to Oxymorphone Base

A hydrogenation vessel is charged with 35 g of water, 17 g of acetic acid and 38.08 g of 14-hydroxymorphinone, prepared in Example 1.2A. The reaction mixture is stirred until a clear solution is obtained before 1.8 g of wet 5% Pd on carbon catalyst is added under a stream of nitrogen. Hydrogen is supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 4 hours. The reaction vessel is cooled to less than 25° C., and a sample is analyzed by HPLC to check for 14-hydroxymorphinone. The 14-hydroxymorphinone area detected by HPLC is 0.26%.

Once it is assessed that the reaction is complete, the catalyst is filtered off and the cake is washed with 15 mL of water. 180 mL of dichloromethane/methanol (9:1, v/v) are added to the filtrate and the pH of the mixture is adjusted to pH 9-10 by adding concentrated ammonium hydroxide. The dichloromethane/methanol layer is separated and purified by slurrying with ca. 20 g florisil. The slurry is filtered and the filtrate is distilled to exchange into n-propanol, and the mixture is cooled to 0-5° C. and stirred for 1-2 hours to precipitate oxymorphone base, which is isolated by filtration. The oxymorphone base is then slurried from n-propanol providing product in 74% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.32% by area.

Example 2.2C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 2.5 g of oxymorphone base, prepared as in Example 2.2B, together with 7.5 mL of absolute alcohol, 2.5 g of water and 1.66 g of concentrated hydrochloric acid. The mixture is heated to 50-60° C. and a solution results. The pH is checked to ensure that it is <1.0. 0.111 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 21 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through a 0.45 μm filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is filtered off, washed with cold absolute alcohol and dried under vacuum to afford white crystals in 77% yield.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 2.8 ppm.

Example 3.1B

Reduction of 14-hydroxymorphinone to Oxymorphone Hydrochloride

The procedure for forming the oxymorphinone free base is followed as shown above, but instead of isolating the free base from a dichloromethane/methanol solution, 0.35 volume equivalents of 3N hydrochloric acid are added (vs the volume of the dichloromethane/methanol solution), the reaction mixture is stirred, allowed to stand, and the aqueous layer (contains the product) is separated from the organic layer. The aqueous layer is distilled under vacuum to remove ca. 50% of the volume, and then the remaining solution is cooled over 2 hour to 20-25° C., stirred for 1-2 hours, cooled to 0-5° C. and stirred 2-3 hours. The white solids that form during stirring are filtered off and washed with cold isopropanol. The yield is 64% and the product contains 0.34% of alpha, beta unsaturated ketones.

Example 3.1C

Purification of Oxymorphone Hydrochloride

Using an analogous process to Example 1.1C, but starting from the product of Example 3.1B, purified oxymorphone hydrochloride is obtained in a yield of 92% and having an undetectable content of alpha, beta unsaturated ketones.

Example 3.2C

Preparation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 5.05 g of oxymorphone hydrochloride, prepared in Example 3.1B, together with 13.5 mL of absolute alcohol, 4.5 mL of water and 1.51 g of concentrated hydrochloric acid. The mixture is heated to 50-60° C. and a solution results. The pH is checked to ensure that it is <1.0. 0.21 g of 10% Pd on charcoal catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through a 0.45 μm filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form a precipitate. The precipitate is collected by filtration, washed with cold absolute alcohol then dried. Yield is 92%.

A sample of the product is tested by HPLC and found to have an undetectable content of alpha, beta unsaturated ketones.

Without changing the basic process steps, but with small variations in the process steps for starting materials, such as isolation or not of such starting materials, and utilising the essential reduction requirements of the invention for the final step to the purified oxymorphone hydrochloride, other products have been obtained with levels of alpha, beta unsaturated ketones of 3.8 ppm, 1.7 ppm, 6.2 ppm, 6.9 ppm, 2.8 ppm, 3.1 ppm, 0.9 ppm, 6.0 ppm and another undetectable, or zero.

Example 3.2D

Hydration of Oxymorphone Hydrochloride

A drying dish is charged with oxymorphone hydrochloride, prepared as in Example 1.1C, 1.2C, 2.2C, 3.1C or 3.2C, which contains about 5-13 wt % of ethanol. The sample is placed in a vacuum oven along with a dish containing 100 mL of water. A vacuum is applied at 24-29 in Hg and the oven maintained at 20-40° C. for 24 hours. An ethanol-free or low ethanol (approx. 0.04 wt %) product is afforded containing about 10-13 wt % of water. The water absorbed by the sample may be removed in a vacuum oven at 50-55° C. The drying process is stopped when the product's KF is 6-8 wt %. The final hydrated oxymorphone hydrochloride affords a uniform polymorph with a consistent X-ray diffraction pattern.

What is claimed:

1. Oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone.

2. Oxymorphone hydrochloride according to claim 1, wherein the content of 14-hydroxymorphinone is less than 5 ppm.

3. A pharmaceutical formulation comprising at least one pharmaceutically acceptable excipient and the oxymorphone hydrochloride according to claim 1.

4. A method of treating pain comprising administering a pharmaceutical formulation according to claim 3 to a patient in need thereof.

5. A method of purifying a starting material of either oxymorphone or oxymorphone hydrochloride to yield the oxymorphone hydrochloride according to claim 1, comprising exposing the starting material oxymorphone or oxymorphone hydrochloride to hydrogen under reducing conditions in a strongly acid water and alcohol solvent reaction medium at a temperature in the range from 60 to 70° C. for a time sufficient to provide the less than 10 ppm of 14-hydroxymorphinone.

6. The method according to claim 5, wherein the exposing is carried out for a period of at least 20 hours.

7. The method according to claim 5, wherein the reaction medium has a pH of less than 1.

8. The method according to claim 5, wherein the acid is hydrochloric acid.

9. The method according to claim 5, wherein the temperature is approximately 65° C.

10. The method according to claim 5, wherein the starting material oxymorphone or oxymorphone hydrochloride has not been isolated from a reaction mixture in which it is formed.

11. The method according to claim 5, wherein the starting material oxymorphone or oxymorphone hydrochloride has been prepared by a process comprising reduction of 14-hydroxymorphinone.

12. The method according to claim 11, wherein the 14-hydroxymorphinone that is reduced is prepared by a process of hydroxylating oripavine.

13. The method according to claim 12, wherein the oripavine is derived from concentrated poppy straw.

14. The method according to claim 13, wherein the concentrated poppy straw is derived from a high-Thebaine-yielding strain of poppy.

15. The method according to claim 5, comprising the additional steps of subsequently forming crystalline oxymorphone hydrochloride and removing residual alcohol molecules from within the crystal structure of the crystalline oxymorphone hydrochloride by exposing the crystalline oxymorphone hydrochloride to water vapour, such that the residual alcohol molecules are displaced with water molecules.

16. The method according to claim 15, comprising the additional step of removing some of the water molecules from within the crystal structure of the oxymorphone hydrochloride by exposure to reduced pressure.

17. The method according to claim 15, comprising the additional step of removing some of the water molecules from within the crystal structure of the oxymorphone hydrochloride by heating the oxymorphone hydrochloride to a temperature in the range of from 50 to 55° C. under reduced pressure.

18. A method of making hydrated oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone and a KF of 6-8 wt %, comprising exposing a starting material of oxymorphone or oxymorphone hydrochloride to gaseous hydrogen under reducing conditions in a strongly acid water and alcohol solvent reaction medium at a temperature in the range from 60 to 70° C., subsequently forming crystalline oxymorphone hydrochloride, and removing residual alcohol molecules from within the crystal structure of the crystalline oxymorphone hydrochloride by exposing the oxymorphone hydrochloride to water vapour, such that the residual alcohol molecules are displaced with water molecules.

19. Hydrated oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone and having peaks within the following 2θ ranges when analyzed by Powder X-Ray Diffraction: 8.5-9.5, 11.0-12.0, 11.5-12.5, 12.4-13.4, 15.2-16.2, 17.6-18.6, 19.3-20.3, 19.9-20.9, 24.6-25.6, 24.9-25.9, 29.0-30.0 and 31.0-32.0.

20. Oxymorphone hydrochloride prepared by the method of claim 5.

21. Hydrated oxymorphone hydrochloride prepared by the method of claim 18.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 7,851,482 B2
APPLICATION NO.	: 11/866840
DATED	: December 14, 2010
INVENTOR(S)	: Jen-Sen Dung et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 23, line 3, delete "20 ranges" and insert therefor --2Θ ranges--.

Signed and Sealed this
Nineteenth Day of July, 2011

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

Exhibit B

US008192722B2

(12) **United States Patent**
Arkenau-Maric et al.

(10) **Patent No.: US 8,192,722 B2**
(45) **Date of Patent: *Jun. 5, 2012**

(54) **ABUSE-PROOF DOSAGE FORM**

(75) Inventors: **Elisabeth Arkenau-Maric**, Köln (DE); **Johannes Bartholomaus**, Aachen (DE); **Heinrich Kugelmann**, Aachen (DE)

(73) Assignee: **Grunenthal GmbH**, Aachen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 664 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/140,665**

(22) Filed: **Jun. 17, 2008**

(65) **Prior Publication Data**

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(51) **Int. Cl.**

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A61K 9/20	(2006.01)
A61K 49/00	(2006.01)
A61K 9/14	(2006.01)
A01N 43/42	(2006.01)

(52) **U.S. Cl.** **424/10.1**; 424/465; 424/484; 514/282

(58) **Field of Classification Search** 424/10.1, 424/465, 484; 514/282
See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to a dosage form that is thermoformed without discoloration and is safeguarded from abuse, comprising at least one synthetic or natural polymer having a breaking strength of at least 500 N in addition to one or more active substances that could be subject to abuse. The invention also relates to a corresponding method for producing said dosage form.

27 Claims, 2 Drawing Sheets

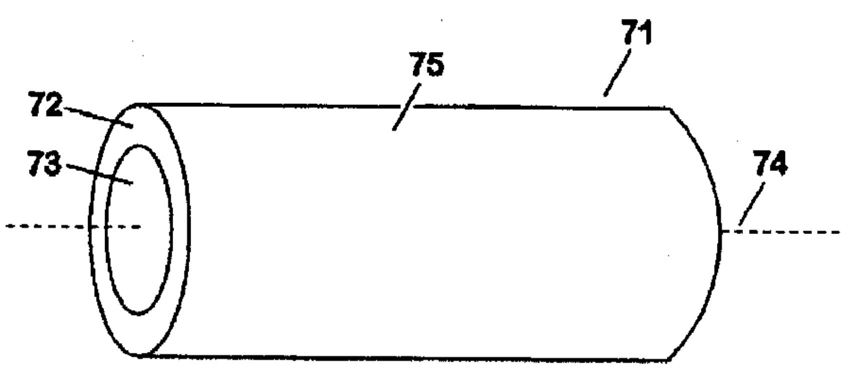

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Figure 1

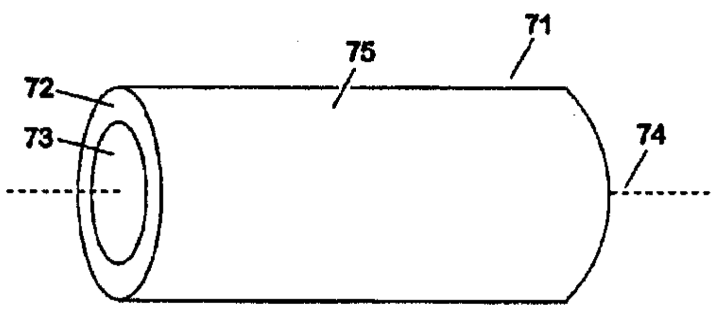


Figure 2A

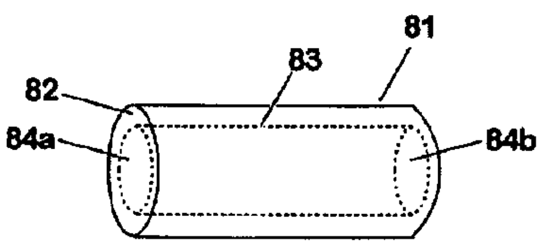


Figure 2B

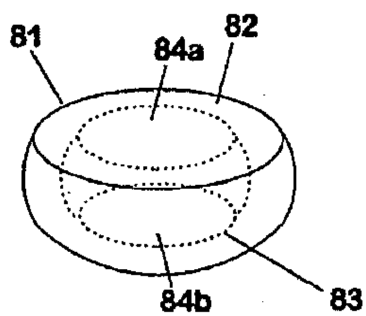
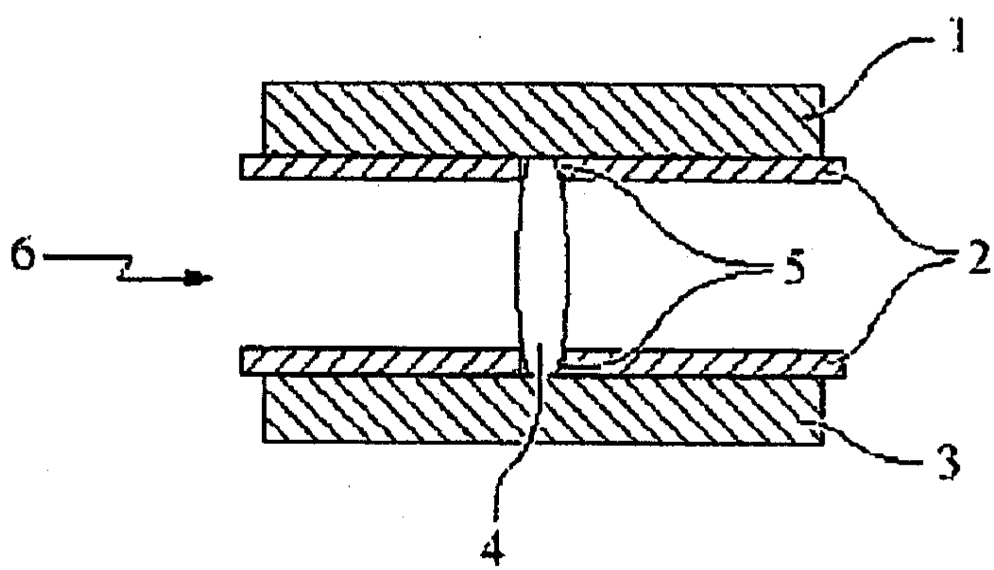


Figure 3



ABUSE-PROOF DOSAGE FORM

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a division of U.S. Ser. No. 11/462,216, filed Aug. 3, 2006, now pending, which is, in turn, a continuation-in-part of U.S. Ser. No. 11/349,544, filed Feb. 6, 2006, and a continuation-in-part of U.S. Ser. No. 11/348,295, filed Feb. 6, 2006, and a continuation-in-part of U.S. Ser. No. 10/718,112, filed Nov. 20, 2003, and also claims priority of German Patent Application No. 10 2005 005446.3 filed on Feb. 4, 2005, and German Patent Application No. 10 336 400.5, filed on Aug. 6, 2003.

BACKGROUND OF THE INVENTION

The present invention relates to an abuse-proofed dosage form thermoformed by extrusion without discoloration and containing, in addition to one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein the dosage form exhibits a breaking strength (=resistance to crushing) of at least 500 N, and to a process for the production of the dosage form according to the invention.

Many pharmaceutical active ingredients, in addition to having excellent activity in their appropriate application, also have abuse potential, i.e. they can be used by an abuser to bring about effects other than those intended. Opiates, for example, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria.

In order to make abuse possible, the corresponding dosage forms, such as tablets or capsules are comminuted, for example ground in a mortar, by the abuser, the active ingredient is extracted from the resultant powder using a preferably aqueous liquid and the resultant solution, optionally after being filtered through cotton wool or cellulose wadding, is administered parenterally, in particular intravenously. An additional phenomenon of this kind of administration, in comparison with abusive oral administration, is a further accelerated increase in active ingredient levels giving the abuser the desired effect, namely the "kick" or "rush". This kick is also obtained if the powdered dosage form is administered nasally, i.e. is sniffed. Since controlled-release dosage forms containing active ingredients with abuse potential do not give rise to the kick desired by the abuser when taken orally even in abusively high quantities, such dosage forms are also comminuted and extracted in order to be abused.

U.S. Pat. No. 4,070,494 proposed adding a swellable agent to the dosage form in order to prevent abuse. When water is added to extract the active ingredient, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredient.

The multilayer tablet disclosed in WO 95/20947 is based on a similar approach to preventing parenteral abuse, said tablet containing the active ingredient with abuse potential and at least one gel former, each in different layers.

WO 03/015531 A2 discloses another approach to preventing parenteral abuse. A dosage form containing an analgesic opioid and a dye as an aversive agent is described therein. The color released by tampering with the dosage form is intended to discourage the abuser from using the dosage form which has been tampered with.

Another known option for complicating abuse involves adding antagonists to the active ingredients to the dosage

form, for example naloxone or naltexone in the case of opioids, or compounds which cause a physiological defense response, such as for example ipecacuanha (ipecac) root.

However, since in most cases of abuse it is still necessary to pulverize the dosage form comprising an active ingredient suitable for abuse, it is an object of the present invention to complicate or prevent the pulverization preceding abuse of the dosage form using the means conventionally available to a potential abuser.

It is a further object to provide a dosage form for active ingredients with potential for abuse which ensures the desired therapeutic effect when correctly administered, but from which the active ingredients cannot be converted into a form suitable for abuse simply by pulverization.

An additional object is to provide a dosage form with enhanced stability when maintained under adverse conditions.

Yet another object is to provide an extrusion process for the manufacture of dosage forms having enhanced abuse prevention and stability characteristics.

A further object is to provide a dosage form having a surface morphology different from that of the core of the dosage form.

An additional object is to provide a dosage form having a non-uniform morphology in general and in particular a dosage form having a layered morphology, in each case where the composition of the dosage form remains uniform.

SUMMARY OF THE INVENTION

These objects have been achieved by the provision of the abuse-proofed dosage form thermoformed by extrusion without discoloration according to the invention which contains, in addition to one or more active ingredients with abuse potential (A), at least one synthetic or natural polymer (C) optionally at least one wax (D), and optionally at least one physiologically acceptable auxiliary substance (B), wherein the dosage form exhibits a breaking strength of at least 500 N.

The breaking strength of at least 500 N (measured as stated in the specification) means that pulverization of the dosage form is considerably more difficult using conventional means, so considerably complicating or preventing the subsequent abuse.

If comminution is inadequate, parenteral, in particular intravenous, administration cannot be performed safely or extraction of the active ingredient therefrom takes too long for the abuser or there is no "kick" when taken orally, as release is not instantaneous.

As used herein, comminution means pulverization of the dosage form with conventional means which are available to an abuser, such as, for example, a mortar and pestle, a hammer, a mallet or other usual means for pulverization by application of force.

The dosage form according to the invention is thus suitable for preventing parenteral, nasal and/or oral abuse of active ingredients, preferably of pharmaceutical active ingredients, with abuse potential.

The advantageous properties of the dosage form according to the invention, in particular also its mechanical properties, may not automatically be achieved by simply processing components (A), (C), optionally (B) and optionally (D) by means of conventional methods for the preparation of dosage forms. In fact, usually suitable apparatuses must be selected for the preparation and critical processing parameters must be adjusted, particularly pressure/force, temperature and time. Dosage forms exhibiting the desired properties may be obtained only if in the course of the preparation of the dosage

form the components are exposed to a sufficient pressure at a sufficient temperature for a sufficient period of time. Thus, although it may be possible to utilize conventional apparatuses, the process protocols usually must be adapted in order to meet the required criteria.

Unlike prior art methods which involve the extrusion of polymers in admixture with pharmaceutically active substances but which fail to provide the dosage forms with the beneficial characteristics according to the present invention because unsuitable extruder types are chosen and/or improper extrusion parameters are adjusted, it has now been discovered that the combination of specific extruder type coupled with herein specified extrusion process parameters provides dosage forms with the enhanced properties disclosed herein.

For example, U.S. Pat. No. 6,488,963 relates to pharmaceutical formulations comprising a hot-melt extrudable mixture of a therapeutic compound and a high molecular weight poly(ethylene oxide). It is disclosed that any commercially available extruder model equipped to handle dry feed and having a solid conveying zone, one or multiple heating zones, and an extrusion die may be used. A single screw extruder is preferred and used in the examples. Besides hot-melt extrusion, other equivalent processes such as injection molding, hot dipping, melt casting and compression molding are said to be useful. The pharmaceutical formulations obtained by the extrusion process according to U.S. Pat. No. 6,488,963, however, fundamentally differ from the dosage forms according to the present invention. This becomes directly evident from the further processing of the extrudate of Example 2 of U.S. Pat. No. 6,488,963, which, upon exiting the die, may be chopped to the desired length and then be ground to a powder. According to U.S. Pat. No. 6,488,963, such powders are preferred for oral, buccal, and sublingual administration.

In contrast to the grindable pharmaceutical formulations according to U.S. Pat. No. 6,488,963, it is an essential feature of the dosage forms according to the present invention that they exhibit a breaking strength of at least 500 N thereby preventing them from being ground to a powder. In the preparation of the dosage forms according to the invention, a suitable extruder type has to be chosen and the extrusion parameters have to be properly adjusted in order to achieve a breaking strength of at least 500 N. In general, single screw extruders of the type disclosed in U.S. Pat. No. 6,488,963 are not suitable to produce the dosage forms according to the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a schematic view of the extrudate of the composition.

FIGS. 2A and 2B show schematic views of the preferred arrangements of the tubular domain within the dosage form.

FIG. 3 shows the measurement of the breaking strength of a tablet.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutical active ingredients with abuse potential are known to the person skilled in the art, as are the quantities thereof to be used and processes for the production thereof, and may be present in the dosage form according to the invention as such, in the form of the corresponding derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof, as racemates or stereoisomers. The dosage form according to the invention is also suitable for the administration of two or more pharmaceutical active ingredients in one dosage form. The dosage form preferably contains just one specific active ingredient.

The dosage form according to the invention is in particular suitable for preventing abuse of a pharmaceutical active ingredient selected from the group consisting of opioids, tranquillizers, preferably benzodiazepines, barbiturates, stimulants and other narcotics.

The dosage form according to the invention is very particularly suitable for preventing abuse of an opioid, tranquillizer or another narcotic selected from the group consisting of N-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl}propionanilide (alfentanil), 5,5-diallylbarbituric acid (allobarbital), allylprodine, alphaprodine, 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepine (alprazolam), 2-diethylaminopropiophenone (amfepramone), (±)-α-methylphenethylamine (amphetamine), 2-(α-methylphenethylamino)-2-phenylacetonitrile (amphetaminil), 5-ethyl-5-isopentylbarbituric acid (amobarbital), anileridine, apocodeine, 5,5-diethylbarbituric acid (barbital), benzylmorphine, bezitramide, 7-bromo-5-(2-pyridyl)-1H-1,4-benzodiazepine-2(3H)-one (bromazepam), 2-bromo-4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo-[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5a-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-endo-ethanomorphinan-3-ol (buprenorphine), 5-butyl-5-ethylbarbituric acid (butobarbital), butorphanol, (7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl) dimethylcarbamate (camazepam), (1S,2S)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), 7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-ylamine 4-oxide (chlordiazepoxide), 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)-dione (clobazam), 5-(2-chlorophenyl)-7-nitro-1H-1,4-benzodiazepin-2(3H)-one (clonazepam), clonitazene, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid (clorazepate), 5-(2-chlorophenyl)-7-ethyl-1-methyl-1H-thieno[2,3-e][1,4]diazepin-2(3H)-one (clotiazepam), 10-chloro-11β-(2-chlorophenyl)-2,3,7,11β-tetrahydrooxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one (cloxazolam), (−)-methyl-[3β-benzoyloxy-2β(1αH,5αH)-tropancarboxylate] (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinan-6α-ol (codeine), 5-(1-cyclohexenyl)-5-ethylbarbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2(3H)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionate (dextropropoxyphen), dezocine, diampromide, diamorphone, 7-chloro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (diazepam), 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6α-morphinandiol (dihydromorphine), dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, (6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (dronabinol), eptazocine, 8-chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (estazolam), ethoheptazine, ethylmethylthiambutene, ethyl [7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepine-3-carboxylate] (ethyl loflazepate), 4,5α-epoxy-3-ethoxy-17-methyl-7-morphinen-6α-ol (ethylmorphine), etonitazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-endo-etheno-morphinan-3-ol (etorphine), N-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methylphenethylamino)ethyl]-theophylline) (fenethylline), 3-(α-methylphenethylamino)propionitrile (fenproporex),

N-(1-phenethyl-4-piperidyl)propionanilide (fentanyl), 7-chloro-5-(2-fluorophenyl)-1-methyl-1H-1,4-benzodiazepin-2(3H)-one (fludiazepam), 5-(2-fluorophenyl)-1-methyl-7-nitro-1H-1,4-benzodiazepin-2(3H)-one (flunitrazepam), 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2(3H)-one (flurazepam), 7-chloro-5-phenyl-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-2(3H)-one (halazepam), 10-bromo-11β-(2-fluorophenyl)-2,3,7,11β-tetrahydro[1,3]oxazolyl[3,2-d][1,4]benzodiazepin-6(5H)-one (haloxazolam), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethyl morphinane, 11-chloro-8,12β-dihydro-2,8-dimethyl-12β-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione (ketazolam), 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3S,6S)-6-dimethylamino-4,4-diphenylheptan-3-yl acetate (levacetylmethadol (LAAM)), (−)-6-dimethylamino-4,4-diphenol-3-heptanone (levomethadone), (−)-17-methyl-3-morphinanol (levorphanol), levophenacylmorphane, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2H-imidazo[1,2-a][1,4]-benzodiazepin-1(4H)-one (loprazolam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1H-1,4-benzodiazepin-2(3H)-one (lorazepam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1H-1,4-benzodiazepin-2(3H)-one (lormetazepam), 5-(4-chlorophenyl)-2,5-dihydro-3H-imidazo[2,1-a]isoindol-5-ol (mazindol), 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine (medazepam), N-(3-chloropropyl)-α-methylphenethylamine (mefenorex), meperidine, 2-methyl-2-propyltrimethylene dicarbamate (meprobamate), meptazinol, metazocine, methylmorphine, N,α-dimethylphenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenyl-3-heptanone (methadone), 2-methyl-3-o-tolyl-4(3H)-quinazolinone (methaqualone), methyl[2-phenyl-2-(2-piperidyl)acetate] (methylphenidate), 5-ethyl-1-methyl-5-phenylbarbituric acid (methylphenobarbital), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylon), metopon, 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine (midazolam), 2-(benzhydrylsulfinyl)acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinan-3,6α-diol (morphine), myrophine, (±)-trans-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[-b,d]pyran-9(6αH)-one (nabilone), nalbuphine, nalorphine, narceine, nicomorphine, 1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (nimetazepam), 7-nitro-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (nitrazepam), 7-chloro-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (nordazepam), norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the exudation for the plants belonging to the species *Papaver somniferum* (opium), 7-chloro-3-hydroxy-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (oxazepam), (cis-trans)-10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-d][1,4]benzodiazepin-6-(5H)-one (oxazolam), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and parts of plants belonging to the species *Papaver somniferum* (including the subspecies *setigerum*), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), 5-ethyl-5-(1-methylbutyl)-barbituric acid (pentobarbital), ethyl (1-methyl-4-phenyl-4-piperidine carboxylate) (pethidine), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodine, 3-methyl-2-phenylmorpholine (phenmetrazine), 5-ethyl-5-phenylbarbituric acid (phenobarbital), α,α-dimethylphenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propynyl)-1H-1,4-benzodiazepin-2(3H)-one (pinazepam), α-(2-piperidyl)benzhydryl alcohol (pipradrol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-4'-carboxamide (piritramide), 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (prazepam), profadol, proheptazine, promedol, properidine, propoxyphene, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, methyl {3-[4-methoxycarbonyl-4-(N-phenylpropanamido)-piperidino]propanoate} (remifentanil), 5-sec-butyl-5-ethylbarbituric acid (secbutabarbital), 5-allyl-5-(1-methylbutyl)-barbituric acid (secobarbital), N-{4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl}-propionanilide (sufentanil), 7-chloro-2-hydroxy-methyl-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (temazepam), 7-chloro-5-(1-cyclohexenyl)-1-methyl-1H-1,4-benzodiazepin-2(3H)-one (tetrazepam), ethyl (2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate) (tilidine (cis and trans)), tramadol, 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (triazolam), 5-(1-methylbutyl)-5-vinylbarbituric acid (vinylbital), (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexan-1,3-diol, preferably as racemate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutylphenyl)-propionate, 3-(2-dimethylaminomethyl-1-hydroxycyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutylphenyl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, (RR—SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-4-chloro-2-hydroxybenzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2-hydroxy-5-nitrobenzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxycyclohexyl)-phenyl ester and corresponding stereoisomeric compounds, the corresponding derivatives thereof in each case, in particular amides, esters or ethers, and the physiologically acceptable compounds thereof in each case, in particular the salts and solvates thereof, particularly preferably hydrochlorides.

In a preferred embodiment the dosage form according to the invention contains one active substance with abuse potential (A) or more active substance with abuse potentials (A) selected from the group consisting of 1,1-(3-dimethylamino-3-phenylpentamethylen)-6-fluor-1,3,4,9-tetrahydropyrano[3,4-b]indole, in particular its hemicitrate; 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylen]-1,3,4,9-tetrahydropyrano[3,4-b]indole, in particular its citrate; and 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylen]-1,3,4,9-tetrahydropyrano[3,4-b]-6-fluoro-indole, in particular its hemicitrate. These compounds are known, for example, from

WO 2004/043967 or WO 2005/066183. The disclosure of these references is expressly incorporated herein and made a part of this present application.

The amount of the active substance with abuse potential (A), based on the total amount of the dosage form, is preferably within the range from 0.01 to 95 wt.-%, more preferably from 0.5 to 80 wt.-%, still more preferably 1.0 to 70 wt.-%, most preferably 5.0 to 60 wt.-% and in particular 10 to 50 wt.-%. In a preferred embodiment it is more than 20 wt.-%.

The dosage form according to the invention is in particular suitable for preventing abuse of an opioid active ingredient selected from the group comprising oxycodone, hydromorphone, morphine, tramadol and the physiologically acceptable derivatives or compounds thereof, preferably the salts and solvates thereof, preferably the hydrochlorides thereof.

The dosage form according to the invention is furthermore in particular suitable for preventing abuse of an opioid active ingredient selected from the group comprising (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, (1R,2R)-3-(2-dimethylaminoethylcyclohexyl)-phenol, the physiologically acceptable salts thereof, preferably hydrochlorides, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, preferably ethers, esters or amides.

These compounds and processes for the production thereof are described in EP-A-693475 or EP-A-780369. The disclosure of these references is expressly incorporated herein and made a part of this present application.

In order to achieve the necessary breaking strength of the dosage form according to the invention, at least one synthetic or natural polymer (C) is used. The polymer (C) contributes to the breaking strength of the dosage form of at least 500 N, measured using the method disclosed in the specification. At least one polymer selected from the group comprising polyalkylene oxides, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers thereof, and mixtures of at least two of the stated polymers is preferably used for this purpose. High molecular weight thermoplastic polyalkylene oxides are preferred. High molecular weight polyethylene oxides with a molecular weight of at least 0.5 million, preferably of at least 1 million up to 15 million, determined by rheological measurements, are particularly preferred. These polymers have a viscosity at 25° C. of 4500 to 17600 cP, measured on a 5 wt. % aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2/rotational speed 2 rpm), of 400 to 4000 cP, measured on a 2 wt. % aqueous solution using the stated viscosimeter (spindle no. 1 or 3/rotational speed 10 rpm) or of 1650 to 10000 cP, measured on a 1 wt. % aqueous solution using the stated viscosimeter (spindle no. 2/rotational speed 2 rpm).

The polymers are preferably used in powder form. They may be soluble in water.

In order to achieve the necessary breaking strength of the dosage form according to the invention, it is furthermore possible additionally to use at least one natural or synthetic wax (D). The wax (D) contributes to the breaking strength of the dosage form of at least 500 N, measured using the method disclosed in the specification. Waxes with a softening point of at least 60° C. are preferred. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred. Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of at least 80° C. When the wax component is additionally used, it is used together with at least one polymer (C) in quantities such that the dosage form has a breaking strength of at least 500 N.

In a preferred embodiment, the breaking strength of the dosage form amounts to at least 500 N, to at least 600 N, to at least 700 N, to at least 800 N, to at least 900 N, to at least 1000 N or even to at least 1100 N.

Component (C) is preferably used in an amount of 20 to 99.9 wt. %, particularly preferably of at least 30 wt. %, very particularly preferably of at least 40 wt. %, relative to the total weight of the dosage form.

In increasingly preferred embodiments, the dosage form according to the invention has a density of at least 0.80 or at least 0.85 g/cm^3, at least 0.90 or at least 0.95 g/cm^3, at least 1.00, at least 1.05 or at least 1.10 g/cm^3, in the range from 0.80 to 1.35 g/cm^3, and in particular in the range from 0.95 to 1.25 g/cm^3.

The dosage form according to the invention is characterized by a comparatively homogeneous distribution of density. Preferably, the densities of two segments of the dosage form having a volume of 1.0 mm^3 each, deviate from one another by not more than ±10%, or by not more than ±7.5%, or by not more than ±5.0%, most preferably not more than ±2.5%, and in particular not more than ±1.0%.

The dosage form according to the invention is characterized by a comparatively homogeneous distribution of the active substance with abuse potential (A). Preferably, the content of component (A) in two segments of the dosage form having a volume of 1.0 mm^3 each, deviates from one another by not more than ±10%, more preferably not more than more than ±7.5%, still more preferably not more than ±5.0%, most preferably not more than ±2.5%, and in particular not more than ±1.0%.

Preferably, the total weight of the dosage form according to the invention is within the range from 0.01 g to 1.5 g, more preferably 0.05 g to 1.2 g, still more preferably 0.1 g to 1.0 g, most preferably 0.2 g to 0.9 g and in particular 0.25 g to 0.8 g.

Auxiliary substances (B) which may be used are those known auxiliary substances which are conventional for the formulation of solid dosage forms. These are preferably plasticizers, such as polyethylene glycol, auxiliary substances which influence active ingredient release, preferably hydrophobic or hydrophilic, preferably hydrophilic polymers, very particularly preferably hydroxypropylcellulose, and/or antioxidants. Suitable antioxidants are ascorbic acid, butylhydroxyanisole, butylhydroxytoluene, salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, sodium bisulfite, particularly preferably butylhydroxytoluene (BHT) or butylhydroxyanisole (BHA) and α-tocopherol.

The antioxidant is preferably used in quantities of 0.01 to 10 wt. %, preferably of 0.03 to 5 wt. %, relative to the total weight of the dosage form.

The dosage forms according to the invention are distinguished in that, due their hardness, they cannot be pulverized in conventional comminution means available to an abuser, such as a mortar and pestle. This virtually rules out oral or parenteral, in particular intravenous or nasal abuse. However, in order to prevent any possible abuse of the dosage form according to the invention, the dosage forms according to the invention may, in a preferred embodiment, contain further agents which complicate or prevent abuse as auxiliary substances (B).

The abuse-proofed dosage form according to the invention, which comprises, apart from one or more active ingredients with abuse potential, at least one hardening polymer (C) and

optionally at least one wax (D), may accordingly also comprise at least one of the following components (a)-(e) as auxiliary substances (B):

at least one substance which irritates the nasal passages and/or pharynx,

at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

at least one antagonist for each of the active ingredients with abuse potential,

at least one emetic,

at least one dye as an aversive agent,

at least one bitter substance.

Components (a) to (f) are additionally each individually suitable for abuse-proofing the dosage form according to the invention. Accordingly, component (a) is preferably suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Combined use according to the invention of at least one of the above-stated components makes it possible still more effectively to prevent abuse of dosage forms according to the invention.

In one embodiment, the dosage form according to the invention may also comprise two or more of components (a)-(f) in a combination, preferably (a), (b) and optionally (c) and/or (f) and/or (e) or (a), (b) and optionally (d) and/or (f) and/or (e).

In another embodiment, the dosage form according to the invention may comprise all of components (a)-(f).

If the dosage form according to the invention comprises component (a) to counter abuse, substances which irritate the nasal passages and/or pharynx which may be considered according to the invention are any substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the abuser that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding active ingredient, for example due to increased nasal secretion or sneezing. These substances which conventionally irritate the nasal passages and/or pharynx may also bring about a very unpleasant sensation or even unbearable pain when administered parenterally, in particular intravenously, such that the abuser does not wish to or cannot continue taking the substance.

Particularly suitable substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli. Appropriate substances and the quantities thereof which are conventionally to be used are known per se to the person skilled or may be identified by simple preliminary testing.

The substance which irritates the nasal passages and/or pharynx of component (a) is preferably based on one or more constituents or one or more plant parts of at least one hot substance drug.

Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie—Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq. The disclosure of these references is expressly incorporated herein and made a part of this present application.

A dosage unit is taken to mean a separate or separable administration unit, such as for example a tablet or a capsule.

One or more constituents of at least one hot substance drug selected from the group consisting of *Allii sativi bulbus* (garlic), *Asari rhizoma cum herba* (Asarum root and leaves), *Calami rhizoma* (calamus root), *Capsici fructus* (capsicum), *Capsici fructus acer* (cayenne pepper), *Curcumae longae rhizoma* (turmeric root), *Curcumae xanthorrhizae rhizoma* (Javanese turmeric root), *Galangae rhizoma* (galangal root), *Myristicae semen* (nutmeg), *Piperis nigri fructus* (pepper), *Sinapis albae semen* (white mustard seed), *Sinapis nigri semen* (black mustard seed), *Zedoariae rhizoma* (zedoary root) and *zingiberis rhizoma* (ginger root), particularly preferably from the group consisting of *Capsici fructus* (capsicum), *Capsici fructus acer* (cayenne pepper) and *Piperis nigri fructus* (pepper) may preferably be added as component (a) to the dosage form according to the invention.

The constituents of the hot substance drugs preferably comprise o-methoxy(methyl)phenol compounds, acid amide compounds, mustard oils or sulfide compounds or compounds derived therefrom.

Particularly preferably, at least one constituent of the hot substance drugs is selected from the group consisting of myristicin, elemicin, isoeugenol, α-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, capsaicin derivatives, such as N-vanillyl-9E-octadecenamide, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, norcapsaicin and nomorcapsaicin, piperine, preferably transpiperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulfonyl mustard oil, and compounds derived from these constituents.

The dosage form according to the invention may preferably contain the plant parts of the corresponding hot substance drugs in a quantity of 0.01 to 30 wt. %, particularly preferably of 0.1 to 0.5 wt. %, in each case relative to the total weight of the dosage unit.

If one or more constituents of corresponding hot substance drugs are used, the quantity thereof in a dosage unit according to the invention preferably amounts to 0.001 to 0.005 wt. %, relative to the total weight of the dosage unit.

Another option for preventing abuse of the dosage form according to the invention consists in adding at least one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel is virtually impossible to administer safely and preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid.

For the purposes of the present invention, visually distinguishable means that the active ingredient-containing gel formed with the assistance of a necessary minimum quantity of aqueous liquid, when introduced, preferably with the assistance of a hypodermic needle, into a further quantity of aqueous liquid at 37° C., remains substantially insoluble and cohesive and cannot straightforwardly be dispersed in such a manner that it can safely be administered parenterally, in particular intravenously. The material preferably remains visually distinguishable for at least one minute, preferably for at least 10 minutes.

The increased viscosity of the extract makes it more difficult or even impossible for it to be passed through a needle or injected. If the gel remains visually distinguishable, this means that the gel obtained on introduction into a further quantity of aqueous liquid, for example by injection into blood, initially remains in the form of a largely cohesive thread, which, while it may indeed be broken up into smaller fragments, cannot be dispersed or even dissolved in such a manner that it can safely be administered parenterally, in particular intravenously. In combination with at least one optionally present component (a) to (e), this additionally leads to unpleasant burning, vomiting, bad flavor and/or visual deterrence.

Intravenous administration of such a gel would most probably result in obstruction of blood vessels, associated with serious harm to the health of the abuser.

In order to verify whether a viscosity-increasing agent is suitable as component (b) for use in the dosage form according to the invention, the active ingredient is mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25° C. If this results in the formation of a gel which fulfils the above-stated conditions, the corresponding viscosity-increasing agent is suitable for preventing or averting abuse of the dosage forms according to the invention.

If component (b) is added to the dosage form according to the invention, one or more viscosity-increasing agents are used which are selected from the group comprising microcrystalline cellulose containing carboxymethylcellulose sodium (e.g. Avicel® RC 591, FMC Corporation, Philadelphia, Pa., US), carboxymethylcellulose sodium (Blanose® Hercules Inc., Wilmington, US; CMC-Na C300P®, Cesalpinia Food S.p.A., Milano, IT; Frimulsion BLC-5®, Cesalpinia Food S.p.A., Milano, IT; Tylose C300 P® SE Tylose GmbH & Co. KG, Wiesbaden, DE), polyacrylic acid (Carbopol® 980 NF, Noveon IP Holdings Corp., Cleveland, Ohio, US, Carbopol® 981, Noveon IP Holdings Corp., Cleveland, Ohio, US), locust bean flour (Cesagum® LA-200, Cesalpinia Food S.p.A., Milano, IT; Cesagum® LID/150, Cesalpinia Food S.p.A., Milano, IT; Cesagum® LN-1, Cesalpinia Food S.p.A., Milano, IT), pectins, preferably from citrus fruits or apples (Cesapectin® HM Medium Rapid Set, Cesalpinia Food S.p.A., Milano, IT), waxy maize starch (C*Gel 04201®, Cerestar Deutschland GmbH, Krefeld, DE), sodium alginate (Frimulsion ALG (E401)®, Cesalpinia Food S.p.A., Milano, IT), guar flour (Frimulsion BM®, Cesalpinia Food S.p.A., Milano, IT; Polygum 26/1-75®, Polygal AG, Marstetten, CH), iota carrageen (Frimulsion D021®, Cesalpinia Food S.p.A., Milano, IT), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®, CP Kelco ApS, Lille Skensved, DK), galactomannan (Meyprogat 150®, Meyhall Chemical, Kreuzlingen, CH), tara bean flour (Polygum 43/1®, Polygal AG, Marstetten, CH), propylene glycol alginate (Protanal-Ester SD-LB®, FCM Biopolymer AS, Drammen, NO), sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200® Unipektin AG, Zurich, CH), fermented polysaccharide welan gum (K1A96), xanthan gum (Xantural 180®). Xanthans are particularly preferred. The names stated in brackets are the trade names by which the materials are known commercially. In general, a quantity of 0.1 to 20 wt. %, particularly preferably of 0.1 to 15 wt. % of the stated viscosity-increasing agent(s) is sufficient to fulfill the above-stated conditions

The component (b) viscosity-increasing agents, where provided, are preferably present in the dosage form according to the invention in quantities of ≧5 mg per dosage unit, i.e. per administration unit.

In a particularly preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) are those which, on extraction from the dosage form with the necessary minimum quantity of aqueous liquid, form a gel which encloses air bubbles. The resultant gels are distinguished by a turbid appearance, which provides the potential abuser with an additional optical warning and discourages him/her from administering the gel parenterally.

Component (C) may also optionally serves as an additional viscosity-increasing agent which, with the assistance of a minimum necessary quantity of an aqueous liquid, forms a gel.

It is also possible to formulate the viscosity-increasing agent and the other constituents in the dosage form according to the invention in a mutually spatially separated arrangement.

In order to discourage and prevent abuse, the dosage form according to the invention may furthermore comprise component (c), namely one or more antagonists for the active ingredient or active ingredients with abuse potential, wherein the antagonists are preferably spatially separated from the remaining constituents of the invention dosage according to the form and, when correctly used, do not exert any effect.

Suitable antagonists for preventing abuse of the active ingredients are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

If the active ingredient present in the dosage form is an opioid, the antagonist used is preferably an antagonist selected from the group comprising naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate. The corresponding antagonists, where component (c) is provided, are preferably used in a quantity of ≧1 mg, particularly preferably in a quantity of 3 to 100 mg, very particularly preferably in a quantity of 5 to 50 mg per dosage form, i.e. per administration unit.

If the dosage form according to the invention comprises a stimulant as active ingredient, the antagonist is preferably a neuroleptic, preferably at least one compound selected from the group consisting of haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopentixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

The dosage form according to the invention preferably comprises these antagonists in a conventional therapeutic dose known to the person skilled in the art, particularly preferably in a quantity of twice to four times the conventional dose per administration unit.

If the combination to discourage and prevent abuse of the dosage form according to the invention comprises component (d), it may comprise at least one emetic, which is preferably present in a spatially separated arrangement from the other components of the dosage form according to the invention and, when correctly used, is intended not to exert its effect in the body.

Suitable emetics for preventing abuse of an active ingredient are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding

physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

An emetic based on one or more constituents of ipecacuanha (ipecac) root, preferably based on the constituent emetine may preferably be considered in the dosage form according to the invention, as are, for example, described in "Pharmazeutische Biologie—Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York, 1982. The disclosure of these references is expressly incorporated herein and made a part of this present application.

The dosage form according to the invention may preferably comprise the emetic emetine as component (d), preferably in a quantity of ≧3 mg, particularly preferably of ≧10 mg and very particularly preferably in a quantity of ≧20 mg per dosage form, i.e. administration unit.

Apomorphine may likewise preferably be used as an emetic in the abuse-proofing according to the invention, preferably in a quantity of preferably ≧3 mg, particularly preferably of ≧5 mg and very particularly preferably of ≧7 mg per administration unit.

If the dosage form according to the invention contains component (e) as a further abuse-preventing auxiliary substance, the use of a such a dye brings about an intense coloration of a corresponding aqueous solution, in particular when the attempt is made to extract the active ingredient for parenteral, preferably intravenous administration, which coloration may act as a deterrent to the potential abuser. Oral abuse, which conventionally begins by means of aqueous extraction of the active ingredient, may also be prevented by this coloration. Suitable dyes and the quantities required for the necessary deterrence may be found in WO 03/015531. The disclosure of this reference is expressly incorporated herein and made a part of this present application.

If the dosage form according to the invention contains component (f) as a further abuse-preventing auxiliary substance, this addition of at least one bitter substance and the consequent impairment of the flavor of the dosage form additionally prevents oral and/or nasal abuse.

Suitable bitter substances and the quantities effective for use may be found in US-2003/0064099 A1. The disclosure of this reference is expressly incorporated herein and made a part of this present application. Suitable bitter substances are preferably aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate (Bitrex®). Denatonium benzoate is particularly preferred.

The solid dosage form according to the invention is suitable to be taken orally, vaginally or rectally, preferably orally. The dosage form is preferably not in film form.

The dosage form according to the invention may assume multiparticulate form, preferably in the form of microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets, optionally packaged in capsules or pressed into tablets, preferably for oral administration. The multiparticulate forms preferably have a size or size distribution in the range from 0.1 to 3 mm, particularly preferably in the range from 0.5 to 2 mm. Depending on the desired dosage form, conventional auxiliary substances (B) are optionally also used for the formulation of the dosage form.

The solid, abuse-proofed dosage form according to the invention is preferably produced by thermoforming with the assistance of an extruder without any observable consequent discoloration of the extrudates.

In order to investigate the extent of discoloration due to this thermoforming, the color of the mixture of starting components of which the dosage form consists is first determined without addition of a color-imparting component, such as for example a coloring pigment or an intrinsically colored component (for example α-tocopherol). This composition is then thermoformed according to the invention, wherein all process steps, including cooling of the extrudate, are preferably performed under an inert gas atmosphere. By way of comparison, the same composition is produced by the same process, but without an inert gas atmosphere. The color of the dosage form produced according to the invention from the starting composition and of the dosage form produced by way of comparison is determined. The determination is performed with the assistance of "Munsell Book of Color" from Munsell Color Company Baltimore, Md., USA, 1966 edition. If the color of the dosage form thermoformed according to the invention has a color with identification no. N 9.5, but at most a color with the identification no. 5Y 9/1, thermoforming is classed as being "without discoloration". If the dosage form has a color with the identification no. 5Y 9/2 or greater, as determined according to the Munsell Book of Color, the thermoforming is classed as being "with discoloration".

Surprisingly, the dosage forms according to the invention exhibit no discoloration classed in accordance with the above classification, if the entire production process is performed under an inert gas atmosphere, preferably under a nitrogen atmosphere with the assistance of an extruder for thermoforming.

In one embodiment of the present invention the abuse-proofed dosage forms are produced by a process comprising

mixing components (A), the optionally present component (B), (C) and the optionally present component (D) and co-mixing the optionally present components a) to f) or, if necessary, separately mixing with the addition of component (C) and optionally (D),

heating the resultant mixture or the resultant mixtures in the extruder at least up to the softening point of component (C) and extruding the mixture through the outlet orifice of the extruder by application of force,

singulating and forming the still plastic extrudate into the dosage form or

cooling and forming the extrudate into the dosage form,

wherein process steps II) and III) and optionally process steps I) and IV) are optionally performed under an inert gas atmosphere, preferably a nitrogen atmosphere.

Mixing of the components according to process step I) may also proceed in the extruder.

Mixing of components (A), optionally (B), (C) and optionally (D) and of the optionally present further components (a)-(f) and optionally components (C) and the optionally present component (D) may also optionally proceed in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

Before blending with the remaining components, component (C) and the optionally present component (D) is preferably provided according to the invention with an antioxidant. This may proceed by mixing the two components, (C) and the antioxidant, preferably by dissolving or suspending the antioxidant in a highly volatile solvent and homogeneously mixing this solution or suspension with component (C) and the optionally present component (D) and removing the solvent by drying, preferably under an inert gas atmosphere. Alternatively, a physiologically acceptable auxiliary substance (B) or a wax (D) may serve as the solvent, preferably at elevated temperature. For example, when polyethylene glycol is used as a plasticizer, it may be molten or liquefied at moderately

elevated temperature and the antioxidant may be dissolved therein. Under these circumstances the highly volatile solvent can be omitted.

The dosage forms according to the invention which contain subunits with further auxiliary substances which prevent or complicate abuse may be produced by coextruding or separately extruding the mixtures according to step I).

In any event, the, preferably molten, mixture or mixtures which has/have been heated in the extruder at least up to the softening point of component (C) is/are extruded from the extruder through a die with at least one bore.

The process according to the invention is preferably performed using conventional screw extruders, particularly preferably twin-screw-extruders.

The extruder preferably comprises at least two temperature zones, with heating of the mixture at least up to the softening point of component (C) proceeding in the first zone, which is downstream from a feed zone and optionally mixing zone. The throughput of the mixture is preferably from 2.0 kg to 8.0 kg/hour.

After heating at least up to the softening point of component (C), the molten mixture is conveyed with the assistance of the screws, further homogenized, compressed or compacted such that, immediately before emerging from the extruder die, it exhibits a minimum pressure of 5 bar, preferably of at least 10 bar, and is extruded through the die as an extruded strand or strands, depending on the number of bores which the die comprises. The die geometry or the geometry of the bores is freely selectable. The die or the bores may accordingly exhibit a round, oblong or oval cross-section, wherein the round cross-section preferably has a diameter of 0.1 mm to 15 mm and the oblong cross-section preferably has a maximum lengthwise extension of 21 mm and a crosswise extension of 10 mm. Preferably, the die or the bores have a round cross-section. The casing of the extruder used according to the invention may be heated or cooled. The corresponding temperature control, i.e. heating or cooling, is so arranged that the mixture to be extruded exhibits at least an average temperature (product temperature) corresponding to the softening temperature of component (C) and does not rise above a temperature at which the active substance with abuse potential which is to be processed may be damaged. Preferably, the temperature of the mixture to be extruded is adjusted to below 180° C., preferably below 150° C., but at least to the softening temperature of component (C).

In general, the following parameters are critical in extrusion processes and have the consequences described:

1. Throughput (kg Per Hour)

If the throughput is too low the extruder is not correctly filled and the material is stressed thereby affecting the viscosity and the release profile of the final product; if the throughput is too high the load of the extruder is higher than 100% and the extruder shuts down automatically; and if the throughput is tolerable but close to the upper limit significant expansion of the extruded strand occurs (also known as "die swelling").

2. Screw Geometry

A minimum number of kneading elements is required in order to obtain a homogeneous mixture; if the number is too high, the material is stressed thereby affecting the viscosity and the release profile of the final product. The number and lead of the conveying elements influences the homogeneity of the mixture and its residence time in the extruder and controls the increase of the pressure in front of the die. Mixing elements improve the homogeneity of the mixture; and eccentric screw heads allow for a continuous discharge of the extrudate without density variations.

3. Die and Merge Element Geometry

The geometry of the element which merges the extrusion strands in front of the die, and geometry of the die itself, the residence time in said element, and the ratio length of the die to diameter of the die influence the compression of the material thereby affecting the melt pressure. The die pressure depends on revolution, throughput and melt temperature and affects the viscosity and the release profile of the final product.

4. Temperature (Melt Zones)

The feeding cylinder should not be heated to prevent the starting material from melting in the feeder and causing an accumulation. The number of cylinders is variable, the longer the extruder the longer the residence time. The temperature of the cylinders (except feeding cylinder) destroys the material if it is too high: if too low the material does not sufficiently melt thereby resulting in an inhomogeneous mixture and degradation. The die temperature, if separately set too low, causes the "extrusion skin" to not properly form thereby making further processing of the extrudate difficult.

5. Revolution of the Extruder

If the extruder revolution speed is too high the material is stressed thereby affecting the viscosity and the release profile of the final product. If the extruder revolution speed is too low the load of the extruder is higher than 100% and the extruder shuts down automatically; and inter alia the residence time depends on the revolution.

6. Arrangement of Cylinders

The position of feeding cylinder and length of the extruder are important. The degassing should be located close to the feeder in order to avoid air pockets in the product; and if one of the components is thermo-labile it may be separately fed into one of the rear cylinders.

7. Temperature of the Water Cooling

Cooling of the engine and control of the temperature of the extrusion cylinders are important parameters.

The process according to the invention requires the use of suitable extruders, preferably screw extruders. Screw extruders which are equipped with two screws (twin-screw-extruders) are particularly preferred. Single-screw extruders are preferably excluded.

The extrusion is preferably performed so that the expansion of the strand due to extrusion is not more than 50%, i.e. that when using a die with a bore having a diameter of e.g. 6 mm, the extruded strand should have a diameter of not more than 9 mm. More preferably, the expansion of the strand is not more than 40%, still more preferably not more than 35%, most preferably not more than 30% and in particular not more than 25%. It has been surprisingly found that if the extruded material in the extruder is exposed to a mechanical stress exceeding a certain limit, a significant expansion of the strand occurs thereby resulting in undesirable irregularities of the properties of the extruded strand, particularly its mechanical properties.

For example, extrusion may be performed by means of a twin-screw-extruder type Micro 27 GL 40 D (Leistritz, Nürnberg, Germany), screw diameter 18 mm. Screws having eccentric ends may be used. A heatable die with a round bore having a diameter of 8 mm may be used. The entire extrusion process may be performed under nitrogen atmosphere. The extrusion parameters may be adjusted e.g. to the following values: rotational speed of the screws: 100 Upm; delivery rate: 4 kg/h; product temperature: 125° C.; and jacket temperature: 120° C.

After extrusion of the molten mixture and optional cooling of the extruded strand or extruded strands, the extrudates are preferably singulated. This singulation may preferably be

performed by cutting up the extrudates by means of revolving or rotating knives, water jet cutters, wires, blades or with the assistance of laser cutters.

An inert gas atmosphere is not necessary for intermediate or final storage of the optionally singulated extrudate or the final shape of the dosage form according to the invention.

The singulated extrudate may be pelletized with conventional methods or be press-molded into tablets in order to impart the final shape to the dosage form. It is, however, also possible not to singulate the extruded strands and, with the assistance of contrarotating calender rolls comprising opposing recesses in their outer sleeve, to form them into the final shape, preferably a tablet, and to singulate these by conventional methods.

Should the optionally singulated extrudate not immediately be formed into the final shape, but instead cooled for storage, after the period of storage an inert gas atmosphere, preferably a nitrogen atmosphere, may optionally be provided and may be maintained during heating of the stored extrudate up until plasticization and definitive shaping to yield the dosage form.

The application of force in the extruder onto the at least plasticized mixture is adjusted by controlling the rotational speed of the conveying device in the extruder and the geometry thereof and by dimensioning the outlet orifice in such a manner that the pressure necessary for extruding the plasticized mixture is built up in the extruder, preferably immediately prior to extrusion. The extrusion parameters which, for each particular composition, are necessary to give rise to a dosage form with a breaking strength of at least 500 N, may be established by simple preliminary testing.

The process according to the invention involves the extrusion of a composition comprising components (A), (C), optionally (B) and optionally (D). Preferably, extrusion is performed by means of twin-screw-extruders.

It has been surprisingly found that extrudates exhibiting an advantageous morphology are obtainable by means of twin-screw-extruders. It has been found that under suitable conditions the extrudate is surrounded by a shell which may be denoted as "extrusion skin". Said extrusion skin can be regarded as a collar-like or tubular structure forming a circumferential section of the extrudate about its longitudinal extrusion axis so that the outer surface of said collar-like or tubular structure forms the closed shell of the extrudate. Usually, only the front faces of the extrudate are not covered by said extrusion skin.

The extrusion skin surrounds the core of the extrudate in a collar-like or tubular arrangement and preferably is connected therewith in a seamless manner. The extrusion skin differs from said core in its morphology. Usually, the extrusion skin is visible with the naked eye in the cross-section of the extrudate, optionally by means of a microscope, since due to the different morphology of the material forming the extrusion skin and the material forming the core, the optical properties differ as well. It seems that during extrusion the material forming the extrusion skin is exposed to mechanical and thermal conditions differing from the conditions the core of the extrudate is exposed to. In consequence, a heterogeneous morphology of the extruded strand is obtained, which e.g. assumes radial symmetry when an extrusion die having circular shape is used. The material forming the extrusion skin and the material forming the core are usually distinguished by their morphology, preferably, however, not by their composition, particularly not by the relative content of components (A), (C), optionally (B) and optionally (D).

Usually the extrusion skin covers the entire shell of the extrudate like a one-piece collar, independently of what geometry has been chosen for the extrusion die. Therefore, the extrudate may assume circular, elliptic or other cross-sections.

The extrusion skin is preferably characterized by a unitary thickness. Preferably, the thickness of the extrusion skin is within the range from 0.1 to 4.0 mm, more preferably 0.15 to 3.5 mm, still more preferably 0.2 to 3.0 mm, most preferably 0.2 to 2.5 mm and in particular 0.2 to 2.0 mm. In a preferred embodiment the thickness of the extrusion skin in the sum over both opposing sides amounts to 0.5 to 50%, more preferably 1.0 to 40%, still more preferably 1.5 to 35%, most preferably 2.0 to 30% and in particular 2.5 to 25% of the diameter of the extrudate.

FIG. 1 shows a schematic view of extrudate (71) having a collar-like extrusion skin (72) entirely surrounding the core (73) about the longitudinal extrusion axis (74). The outer surface of extrusion skin (72) forms the shell (75) of the extrudate (71).

It has been surprisingly found that extrudates having an extrusion skin exhibit beneficial mechanical properties. They are particularly suitable as intermediates in the production of the dosage forms according to the invention, because they may be advantageously processed, in particular by singulating and/or forming.

When the dosage forms according to the invention are prepared by means of extrusion processes which lead to intermediates having an extrusion skin as described above, the dosage forms obtained therefrom are preferably also characterized by a particular morphology.

In a preferred embodiment those regions, which have formed the extrusion skin in the extruded intermediate, are still visible with the naked eye, optionally by means of a microscope, in the cross-section of the dosage form. This is because usually by further processing the extrudate, particularly by singulating and/or shaping, the different nature and thereby also the different optical properties of the material forming the extrusion skin and the material forming the core are maintained. In the following, that domain of the dosage forms which has emerged from the extrusion skin in the course of further processing the extruded intermediate, will be denoted as "tubular domain".

Preferably, the dosage form according to the invention comprises a tubular domain and a core located therein. Preferably, the tubular domain is connected with the core in a seamless manner. Preferably the tubular domain as well as the core have substantially the same chemical composition, i.e. substantially the same relative content of components (A), (C), optionally (B) and optionally (D). The material forming the tubular domain has a morphology differing from the material forming the core. Usually, this different morphology is also expressed in terms of different optical properties, so that the tubular domain and the core are visible with the naked eye in the cross-section of the dosage form.

In case that the dosage form has been coated, e.g. by a film coating, the tubular domain is located between the film coating and the core.

Since the dosage form according to the invention may be obtained in different ways from the extrudate containing the extrusion skin (intermediate), the tubular domain may take different arrangements and extensions within the dosage form according to the invention. All arrangements have in common, however, that the tubular domain partially covers the surface of the core, but usually not its entire surface. Preferably, two opposing surfaces of the core are not, or at least not fully covered by the tubular domain. In other words, preferably the tubular domain has two openings/blanks on opposing sides.

The thickness of the tubular domain may be uniform. It is also possible, however, that in the course of the processing, i.e. due to the subsequent shaping (e.g. press-forming) of the extrudate, various sections of the extrusion skin are expanded or compressed differently thereby leading to a variation of the thickness of the tubular domain within the dosage form.

Preferably the thickness of the tubular domain is within the range from 0.1 to 4.0 mm, more preferably 0.15 to 3.5 mm, still more preferably 0.2 to 3.0 mm, most preferably 0.2 to 2.5 mm and in particular 0.2 to 2.0 mm.

FIGS. 2A and 2B show schematic views of preferred arrangements of the tubular domain within the dosage form according to the invention. The dosage forms (**81**) contain a tubular domain (**82**) partially surrounding the core (**83**). The opposing surfaces (**84***a*) and (**84***b*) of the core (**83**), however, are not covered by the tubular domain (**82**).

The process for the preparation of the dosage form according to the invention is preferably performed continuously. Preferably, the process involves the extrusion of a homogeneous mixture of components (A), (C), optionally (B) and optionally (D). It is particularly advantageous if the obtained intermediate, e.g. the strand obtained by extrusion, exhibits uniform properties. Particularly desirable are uniform density, uniform distribution of the active substance, uniform mechanical properties, uniform porosity, uniform appearance of the surface, etc. Only under these circumstances the uniformity of the pharmacological properties, such as the stability of the release profile, may be ensured and the amount of rejects can be kept low.

Preferably, the process according to the present invention may be performed with less than 25% rejects, more preferably less than 20%, most preferably less than 15% and in particular less than 10% rejects, wherein the criteria for rejection are the FDA standards regarding the intervariability of the content of component (A), its release profile and/or the density of the dosage form when comparing two dosage forms, preferably taken from the same batch.

It has been surprisingly found that the above properties may be obtained by means of twin-screw-extruders.

The process according to the invention preferably involves the extrusion of a mixture of components (A), (C), optionally (B) and optionally (D), preferably by means of a twin-screw-extruder. After extrusion the extrudate is preferably singulated, shaped and optionally coated in order to obtain the final dosage form.

In a preferred embodiment of the process according to the invention, shaping is performed in the plasticized state of the mixture of components (A), (C), optionally (B) and optionally (D). It has been surprisingly found that the extrusion of certain polymers (C), particular of high molecular weight polyethylene oxides, yields intermediates exhibiting some kind of memory effect: when the singulated extrudates are shaped at ambient temperature, e.g. by press-forming, dosage forms are obtained which tend to regain their original outer form upon storage under stressed storage conditions, i.e. they return to the form they had prior to shaping.

The shape of the dosage form upon storage at stressed conditions, e.g. at 40° C./75% RH, may also be unstable for other reasons.

Said memory effect significantly deteriorates the storage stability of the dosage form, as by regaining its outer form several properties of the dosage form are changed. The same applies to any changes of the outer form due to other reasons.

It has been found that, for example, depending on the extrusion conditions a significant expansion of the strand may occur thereby resulting in an increase of the volume of the extrudate, i.e. a decrease of its density. Said expansion may be compensated by subsequently press-forming the singulated extrudate at a sufficient pressure, since under these conditions the expansion of the material may be reversed.

However, if press-forming has been performed at ambient temperature, the memory effect of the compressed extrudate will cause it to swell and to expand upon storage, thereby significantly increasing the volume of the dosage form.

It has been surprisingly found that such memory effect may be suppressed if shaping of the singulated extrudate is performed at increased temperature, i.e. in the plasticized state of the mixture of components (A), (C), optionally (B) and optionally (D). Preferably, shaping is performed at a pressure of at least 1 kN, more preferably within the range from 2 kN to 50 kN, e.g. by means of a tablet press. Preferably, shaping is performed at a temperature which preferably is about 40° C., more preferably about 30° C. and in particular about 25° C. below the melting range of the mixture of components (A), (C), optionally (B) and optionally (D). The melting range of a given mixture may be determined by conventional methods, preferably by DSC (e.g. with a DSC model 2920 (TA Instruments, New Castle) and ultrahigh pure nitrogen as purge gas at a flow rate of 150 ml/min; approximate sample weight of 10-20 mg, sealed in nonhermetic aluminium pans; temperature ramp speed 10° C./min).

In a preferred embodiment the outer shape of the dosage form according to the invention does not substantially change when being stored for at least 12 h, preferably for at least 24 h, at 40° C. and 75% RH, preferably in an open container.

In a preferred embodiment the volume of the dosage form according to the invention increases by not more than 20% or 17.5%, more preferably not more than 15% or 12.5%, still more preferably not more than 10% or 7.5%, most preferably not more than 6.0%, 5.0% or 4.0% and in particular not more than 3.0%, 2.0% or 1.0% when being stored for at least 12 h, preferably for at least 24 h, at a temperature of 20° C. below the melting range of the mixture of components (A), (C), optionally (B) and optionally (D), optionally at a temperature of 40° C. and 75% RH.

In a further preferred embodiment, the dosage form according to the invention assumes the form of a tablet, a capsule or is in the form of an oral osmotic therapeutic system (OROS), preferably if at least one further abuse-preventing component (a)-(f) is also present.

If components (c) and/or (d) and/or (f) are present in the dosage form according to the invention, care must be taken to ensure that they are formulated in such a manner or are present in such a low dose that, when correctly administered, the dosage form is able to bring about virtually no effect which impairs the patient or the efficacy of the active ingredient.

If the dosage form according to the invention contains component (d) and/or (f), the dosage must be selected such that, when correctly orally administered, no negative effect is caused. If, however, the intended dosage of the dosage form is exceeded in the event of abuse, nausea or an inclination to vomit or a bad flavor are produced. The particular quantity of component (d) and/or (f) which can still be tolerated by the patient in the event of correct oral administration may be determined by the person skilled in the art by simple preliminary testing.

If, however, irrespective of the fact that the dosage form according to the invention is virtually impossible to pulverize, the dosage form containing the components (c) and/or (d) and/or (f) is provided with protection, these components should preferably be used at a dosage which is sufficiently high that, when abusively administered, they bring about an intense negative effect on the abuser. This is preferably

achieved by spatial separation of at least the active ingredient or active ingredients from components (c) and/or (d) and/or (f), wherein the active ingredient or active ingredients is/are present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and wherein, when the dosage form is correctly administered, components (c), (d) and (f) do not exert their effect on taking and/or in the body and the remaining components of the formulation, in particular component (C) and optionally (D), are identical.

If the dosage form according to the invention comprises at least 2 of components (c) and (d) or (f), these may each be present in the same or different subunits (Y). Preferably, when present, all the components (c) and (d) and (f) are present in one and the same subunit (Y).

For the purposes of the present invention, subunits are solid formulations, which in each case, apart from conventional auxiliary substances known to the person skilled in the art, contain the active ingredient(s), at least one polymer (C) and the optionally present component (D) and optionally at least one of the optionally present components (a) and/or (b) and/or (e) or in each case at least one polymer (C) and optionally (D) and the antagonist(s) and/or emetic(s) and/or component (e) and/or component (f) and optionally at least one of the optionally present components (a) and/or (b). Care must here be taken to ensure that each of the subunits is formulated in accordance with the above-stated process.

One substantial advantage of the separated formulation of active ingredients from components (c) or (d) or (f) in subunits (X) and (Y) of the dosage form according to the invention is that, when correctly administered, components (c) and/or (d) and/or (f) are hardly released on taking and/or in the body or are released in such small quantities that they exert no effect which impairs the patient or therapeutic success or, on passing through the patient's body, they are only liberated in locations where they cannot be sufficiently absorbed to be effective. When the dosage form is correctly administered, preferably hardly any of components (c) and/or (d) and/or (f) is released into the patient's body or they go unnoticed by the patient.

The person skilled in the art will understand that the above-stated conditions may vary as a function of the particular components (c), (d) and/or (f) used and of the formulation of the subunits or the dosage form. The optimum formulation for the particular dosage form may be determined by simple preliminary testing. What is vital is that each subunit contains the polymer (C) and optionally component (D) and has been formulated in the above-stated manner.

Should, contrary to expectations, the abuser succeed in comminuting such a dosage form according to the invention, which comprises components (c) and/or (e) and/or (d) and/or (f) in subunits (Y), for the purpose of abusing the active ingredient and obtain a powder which is extracted with a suitable extracting agent, not only the active ingredient but also the particular component (c) and/or (e) and/or (f) and/or (d) will be obtained in a form in which it cannot readily be separated from the active ingredient, such that when the dosage form which has been tampered with is administered, in particular by oral and/or parenteral administration, it will exert its effect on taking and/or in the body combined with an additional negative effect on the abuser corresponding to component (c) and/or (d) and/or (f) or, when the attempt is made to extract the active ingredient, the coloration will act as a deterrent and so prevent abuse of the dosage form.

A dosage form according to the invention, in which the active ingredient or active ingredients is/are spatially separated from components (c), (d) and/or (e), preferably by formulation in different subunits, may be formulated in many different ways, wherein the corresponding subunits may each be present in the dosage form according to the invention in any desired spatial arrangement relative to one another, provided that the above-stated conditions for the release of components (c) and/or (d) are fulfilled.

The person skilled in the art will understand that component(s) (a) and/or (b) which are optionally also present may preferably be formulated in the dosage form according to the invention both in the particular subunits (X) and (Y) and in the form of independent subunits corresponding to subunits (X) and (Y), provided that neither the abuse-proofing nor the active ingredient release in the event of correct administration is impaired by the nature of the formulation and the polymer (C) and optionally (D) is included in the formulation and formulation is carried out in accordance with the above-stated process in order to achieve the necessary hardness.

In a preferred embodiment of the dosage form according to the invention, subunits (X) and (Y) are present in multiparticulate form, wherein microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets are preferred and the same form, i.e. shape, is selected for both subunit (X) and subunit (Y), such that it is not possible to separate subunits (X) from (Y) by mechanical selection. The multiparticulate forms are preferably of a size in the range from 0.1 to 3 mm, preferably of 0.5 to 2 mm.

The subunits (X) and (Y) in multiparticulate form may also preferably be packaged in a capsule or be pressed into a tablet, wherein the final formulation in each case proceeds in such a manner that the subunits (X) and (Y) are also retained in the resultant dosage form.

The multiparticulate subunits (X) and (Y) of identical shape should also not be visually distinguishable from one another so that the abuser cannot separate them from one another by simple sorting. This may, for example, be achieved by the application of identical coatings which, apart from this disguising function, may also incorporate further functions, such as, for example, controlled release of one or more active ingredients or provision of a finish resistant to gastric juices on the particular subunits.

The multiparticulate subunits may also be formulated as an oral dosage form as a slurry or suspension in pharmaceutically safe suspending media.

In a further preferred embodiment of the present invention, subunits (X) and (Y) are in each case arranged in layers relative to one another.

The layered subunits (X) and (Y) are preferably arranged for this purpose vertically or horizontally relative to one another in the dosage form according to the invention, wherein in each case one or more layered subunits (X) and one or more layered subunits (Y) may be present in the dosage form, such that, apart from the preferred layer sequences (X)—(Y) or (X)—(Y)—(X), any desired other layer sequences may be considered, optionally in combination with layers containing components (a) and/or (b).

Another preferred dosage form according to the invention is one in which subunit (Y) forms a core which is completely enclosed by subunit (X), wherein a separation layer (Z) may be present between said layers. Such a structure is preferably also suitable for the above-stated multiparticulate forms, wherein both subunits (X) and (Y) and an optionally present separation layer (Z), which must satisfy the hardness requirement according to the invention, are formulated in one and the same multiparticulate form. In a further preferred embodiment of the dosage form according to the invention, the subunit (X) forms a core, which is enclosed by subunit (Y),

wherein the latter comprises at least one channel which leads from the core to the surface of the dosage form.

The dosage form according to the invention may comprise, between one layer of the subunit (X) and one layer of the subunit (Y), in each case one or more, preferably one, optionally swellable separation layer (Z) which serves to separate subunit (X) spatially from (Y).

If the dosage form according to the invention comprises the layered subunits (X) and (Y) and an optionally present separation layer (z) in an at least partially vertical or horizontal arrangement, the dosage form preferably takes the form of a tablet, a coextrudate or a laminate.

In one particularly preferred embodiment, the entirety of the free surface of subunit (Y) and optionally at least part of the free surface of subunit(s) (X) and optionally at least part of the free surface of the optionally present separation layer(s) (Z) may be coated with at least one barrier layer (Z') which prevents release of component (c) and/or (e) and/or (d) and/or (f). The barrier layer (Z') must also fulfill the hardness conditions according to the invention.

Another particularly preferred embodiment of the dosage form according to the invention comprises a vertical or horizontal arrangement of the layers of subunits (X) and (Y) and at least one push layer (p) arranged therebetween, and optionally a separation layer (z), in which dosage form the entirety of the free surface of layer structure consisting of subunits (X) and (Y), the push layer and the optionally present separation layer (z) is provided with a semipermeable coating (E), which is permeable to a release medium, i.e. conventionally a physiological liquid, but substantially impermeable to the active ingredient and to component (c) and/or (d) and/or (f), and wherein this coating (E) comprises at least one opening for release of the active ingredient in the area of subunit (X).

A corresponding dosage form is known to the person skilled in the art, for example under the name oral osmotic therapeutic system (OROS), as are suitable materials and methods for the production thereof, inter alia from U.S. Pat. Nos. 4,612,008, 4,765,989 and 4,783,337. The disclosure of these references is expressly incorporated herein and made a part of this present application.

In a further preferred embodiment, the subunit (X) of the dosage form according to the invention is in the form of a tablet, the edge face of which and optionally one of the two main faces is covered with a barrier layer (Z') containing component (c) and/or (d) and/or (f).

The person skilled in the art will understand that the auxiliary substances of the subunit(s) (X) or (Y) and of the optionally present separation layer(s) (Z) and/or of the barrier layer(s) (Z') used in formulating the dosage form according to the invention will vary as a function of the arrangement thereof in the dosage form according to the invention, the mode of administration and as a function of the particular active ingredient of the optionally present components (a) and/or (b) and/or (e) and of component (c) and/or (d) and/or (f). The materials which have the requisite properties are in each case known per se to the person skilled in the art.

If release of component (c) and/or (d) and/or (f) from subunit (Y) of the dosage form according to the invention is prevented with the assistance of a cover, preferably a barrier layer, the subunit may consist of conventional materials known to the person skilled in the art, providing that it contains at least one polymer (C) and optionally (D) to fulfill the hardness condition of the dosage form according to the invention.

If a corresponding barrier layer (Z') is not provided to prevent release of component (c) and/or (d) and/or (f), the materials of the subunits should be selected such that release of the particular component (c) and/or (d) from subunit (Y) is virtually ruled out. The materials which are stated below to be suitable for production of the barrier layer may preferably be used for this purpose.

Preferred materials are those which are selected from the group comprising alkylcelluloses, hydroxyalkyl-celluloses, glucans, scleroglucans, mannans, xanthans, copolymers of poly[bis(p-carboxyphenoxy)propane and sebacic acid, preferably in a molar ratio of 20:80 (commercially available under the name Polifeprosan 20®), carboxymethylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid and the esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes and polyurethanes and the copolymers thereof.

Particularly suitable materials may be selected from the group comprising methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, sodium cellulose sulfate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctadecyl acrylate, polyethylene, low density polyethylene, high density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate and polyvinyl chloride.

Particularly suitable copolymers may be selected from the group comprising copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid with high molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride and copolymers of vinyl alcohol and vinyl acetate.

Further materials which are particularly suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20073), aliphatic polyesteramides (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatic and aromatic polyester urethanes (DE 19822979), polyhydroxyalkanoates, in particular polyhydroxybutyrates, polyhydroxyvalerates, casein (DE 4 309 528), polylactides and copolylactides (EP 0 980 894 A1). The disclosure of these references is expressly incorporated herein and made a part of this present application.

The above-stated materials may optionally be blended with further conventional auxiliary substances known to the person skilled in the art, preferably selected from the group comprising glyceryl monostearate, semi-synthetic triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinyl-pyrrolidone, gelatine, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

If the dosage form according to the invention comprises a separation layer (Z'), said layer, like the uncovered subunit (Y), may preferably consist of the above-stated materials described for the barrier layer. The person skilled in the art will understand that release of the active ingredient or of

component (c) and/or (d) from the particular subunit may be controlled by the thickness of the separation layer.

The dosage form according to the invention exhibits controlled release of the active ingredient. It is preferably suitable for twice daily administration to patients.

The release properties of the dosage form according to the invention are substantially independent from the pH value of the release medium, i.e. preferably the release profile in artificial intestinal juice substantially corresponds to the release profile in artificial gastric juice. Preferably, at any given time point the release profiles deviate from one another by not more than 20%, more preferably not more than 15%, still more preferably not more than 10%, yet more preferably not more than 7.5%, most preferably not more than 5.0% and in particular not more than 2.5%.

Preferably, the dosage form according to the invention exhibits a uniform release profile. Preferably, the release profile of the active substance with abuse potential (A) is interindividually uniform (i.e. when comparing dosage forms obtained from the same process) and/or uniform within a single dosage form (i.e. when comparing segments of the same dosage form). Preferably, when comparing two probes each having a mass of preferably 500 mg, the total amount of the released active substance for any given time point of the measurement does not deviate by more than 20%, more preferably not more than 15%, still more preferably not more than 10%, yet more preferably not more than 7.5%, most preferably not more than 5.0% and in particular not more than 2.5%.

Preferably, the release profile of the dosage form according to the present invention is stable upon storage, preferably upon storage at elevated temperature, e.g. 37° C., for 3 month in sealed containers. In this regard "stable" means that when comparing the initial release profile with the release profile after storage, at any given time point the release profiles deviate from one another by not more than 20%, more preferably not more than 15%, still more preferably not more than 10%, yet more preferably not more than 7.5%, most preferably not more than 5.0% and in particular not more than 2.5%.

The dosage form according to the invention may comprise one or more active ingredients at least partially in controlled release form, wherein controlled release may be achieved with the assistance of conventional materials and methods known to the person skilled in the art, for example by embedding the active ingredient in a controlled release matrix or by the application of one or more controlled release coatings. Active ingredient release must, however, be controlled such that the above-stated conditions are fulfilled in each case, for example that, in the event of correct administration of the dosage form, the active ingredient or active ingredients are virtually completely released before the optionally present component (c) and/or (d) can exert an impairing effect. Addition of materials effecting controlled release must moreover not impair the necessary hardness.

Controlled release from the dosage form according to the invention is preferably achieved by embedding the active ingredient in a matrix. The auxiliary substances acting as matrix materials control active ingredient release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which active ingredient release proceeds mainly by diffusion, or hydrophobic materials, from which active ingredient release proceeds mainly by diffusion from the pores in the matrix.

Physiologically acceptable, hydrophobic materials which are known to the person skilled in the art may be used as matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials.

Matrix materials prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also preferred. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials.

It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

Component (C) and the optionally present component (D), which serve to achieve the breaking strength of at least 500 N which is necessary according to the invention may furthermore also optionally serve as additional matrix materials.

If the dosage form according to the invention is intended for oral administration, it may also preferably comprise a coating which is resistant to gastric juices and dissolves as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the dosage form according to the invention passes through the stomach undissolved and the active ingredient is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

Corresponding materials and methods for the controlled release of active ingredients and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms—Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The disclosure of these references is expressly incorporated herein and made a part of this present application.

Method for Determining the Breaking Strength

In order to verify whether a polymer may be used as component (C) or (D), the polymer is pressed to form a tablet with a diameter of 10 mm and a height of 5 mm using a force of 150 N at a temperature which at least corresponds to the softening point of the polymer and is determined with the assistance of a DSC diagram of the polymer. Using tablets produced in this manner, breaking strength is determined with the apparatus described below in accordance with the method for determining the breaking strength of tablets published in the European Pharmacopoeia 1997, page 143-144, method no. 2.9.8. The apparatus used for the measurement is a "Zwick Z 2.5" materials tester, Fmax=2.5 kN with a maximum draw of 1150 mm, which should be set up with 1 column and 1 spindle, a clearance behind of 100 mm and a test speed adjustable between 0.1 and 800 mm/min together with testControl software. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diam. 10 mm), a force transducer, Fmax. 1 kN, diameter=8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M to DIN 55350-18 (Zwick gross force Fmax=1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with order no. BTC-FR 2.5 TH. D09 for the tester, order no. BTC-LC 0050N. P01 for the force transducer, order no. BO 70000 S06 for the centering device.

FIG. 3 shows the measurement of the breaking strength of a tablet, in particular the tablet (4) adjustment device (6) used for this purpose before and during the measurement. To this end, the tablet (4) is held between the upper pressure plate (1) and the lower pressure plate (3) of the force application appa-

ratus (not shown) with the assistance of two 2-part clamping devices, which are in each case firmly fastened (not shown) with the upper and lower pressure plate once the spacing (5) necessary for accommodating and centering the tablet to be measured has been established. The spacing (5) may be established by moving the 2-part clamping devices horizontally outwards or inwards in each case on the pressure plate on which they are mounted.

The tablets deemed to be resistant to breaking under a specific load include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

In the case of the dosage forms according to the invention, breaking strength is determined in accordance with the stated method, dosage forms other than tablets also being tested.

The following Examples illustrate the invention purely by way of example and without restricting the general concept of the invention.

EXAMPLE 1

Components	Per tablet	Per batch
Tramadol HCl	100.0 mg	1495.0 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	167.8 mg	2508.6 g
Hydroxypropylmethylcellulose 100 000 mPa · s	33.5 mg	500.8 g
Polyethylene glycol (PEG 6000)	33.5 mg	500.8 g
Butylhydroxytoluene (BHT)	0.2 mg	3.0 g
Total weight	335.0 mg	5008.2 g

The stated quantity of BHT was dissolved in ethanol (96%), such that a 7.7% (mass/mass) ethanolic solution was obtained. This was mixed initially with 150 g of polyethylene oxide in a high speed mixer for 30 minutes and then the remaining quantity of polyethylene oxide was added and stirring continued for a further 30 minutes. The composition was dried for 12 h at 40° C. All the further components were added and mixed for 15 min in a free-fall mixer. The powder mixture was apportioned into an extruder. Extrusion was performed using a model Micro 27 GL 40 D double screw extruder with a spindle diameter of 18 mm manufactured by Leistritz (Nürnberg). Screws with blunt ends were used, the hex socket at the end of the screws being closed with a cap. The die used is a heatable round die with a diameter of 8 mm. The entire process was performed under an N_2 atmosphere.

The following parameters were selected for extrusion:

Screw speed:	100 rpm
Throughput:	4 kg/h
Product temperature:	125° C.
Casing temperature:	120° C.

The extrudate, which was still hot, was cooled under a nitrogen atmosphere. The cooled strand was singulated into biplanar tablets. The tablets did not break when exposed to a force of 500 N. The tablets could not be comminuted either with a hammer or with the assistance of a mortar and pestle.

The color of the cooled strand or of the 10 tablets singulated therefrom was determined at N 9.5/using the Munsell Book of Color, such that the dosage form produced by the process according to the invention did not exhibit any discoloration due to the thermoforming with the assistance of an extruder.

EXAMPLE 2

Components	Per Tablet	Per batch	
Oxycodon HCl	20.0 mg	410.1 g	13.7%
Polyethylene oxide 7 000 000 (Polyox WSR 303, DOW Chemicals)	107.2 mg	2199.3 g	73.2%
Polyethylene glycol (PEG 6000)	15.0 mg	307.8 g	10.3%
Hypromellose (Metholose 90 SH 100 000 cP, ShinEtsu)	3.8 mg	76.8 g	2.6%
α-Tocopherol	0.2 mg	3.0 g	0.1%
Aerosil (highly disperse SiO_2)	0.2 mg	3.0 g	0.1%
	146.4 mg	3000.0 g	100%

50 g of the polyethylene oxide, 3 g α-tocopherol and 3 g Aerosil were mixed to a homogeneous mixture by means of a mortar. All the further components were added and mixed for 15 minutes in a free-fall mixer.

Extrusion was performed using a model Micro 27 PH 40 D twin screw extruder manufactured by Leistritz (Nürnberg). Screws having eccentric ends were used. The die used is a heatable round die having a diameter of 9 mm.

The following parameters were selected for extrusion:

Screw speed:	100 rpm
Throughput:	4 kg/h
Product temperature:	134° C.
Casing temperature:	heating zones 1 to 10: 100° C. heating zone 11 (die): 120° C.

The extrudate, which was still hot, was cooled. No nitrogen atmosphere was used. The product did not exhibit any yellowish discoloration.

The cooled strand was singulated into biplanar slices. The final press-forming was performed by means on an eccentric tablet press (model EK0). Oblong punches (width 5 mm, length 12 mm) were used as tabletting tool. The respective tablets (mass and form) were punched from the slices and press-formed. One tablet was obtained from one slice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to a force of 500 N. The tablet could not be comminuted with a hammer. This could not be achieved with the assistance of a pestle and mortar either.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur. The temperature of the release medium was 37° C. and the rotational speed of the stirrer 75 min^{-1}. 600 ml of artificial intestinal juice, pH 6.8 were used as release medium. The released quantity of active ingredient present in the dissolution medium at each point in time was determined by spectrophotometry.

Time	Amount Released
60 min	36%
240 min	79%
480 min	99%
720 min	107%

EXAMPLE 3

Components	Per Tablet	Per batch	%
Oxycodon HCl	20.0 mg	333.3 g	11.1
Polyethylene oxide 7 000 000 (Polyox WSR 303, DOW Chemicals)	122.6 mg	2060.7 g	68.7
Polyethylene glycol (PEG 6000)	18.0 mg	300.0 g	10.0
Hypromellose (Metholose 90 SH 100 000 cP, ShinEtsu)	18.0 mg	300.0 g	10.0
α-Tocopherol	0.2 mg	3.0 g	0.1
Aerosil (highly disperse SiO_2)	0.2 mg	3.0 g	0.1
	180 mg	3000.0 g	100%

50 g of the polyethylene oxide, 3 g α-tocopherol and 3 g Aerosil were mixed to a homogeneous mixture by means of a mortar. All the further components were added and mixed for 15 minutes in a free-fall mixer.

Extrusion was performed using a model Micro 27 PH 40 D twin screw extruder manufactured by Leistritz (Nürnberg). Screws having eccentric ends were used. The die used is a heatable round die having a diameter of 9 mm.

The following parameters were selected for extrusion:

Screw speed:	100 rpm
Throughput:	4 kg/h
Product temperature:	134° C.
Casing temperature:	heating zones 1 to 10: 100° C. heating zone 11 (die): 120° C.

The extrudate, which was still hot, was cooled. No nitrogen atmosphere was used. The product did not exhibit any yellowish discoloration.

The cooled strand was singulated into biplanar slices. The final press-forming was performed by means on an eccentric tablet press (model EK0). Oblong punches (width 5 mm, length 12 mm) were used as tabletting tool. The respective tablets (mass and form) were punched from the slices and press-formed. One tablet was obtained from one slice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to a force of 500 N. The tablet could not be comminuted with a hammer. This could not be achieved with the assistance of a pestle and mortar either.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur. The temperature of the release medium was 37° C. and the rotational speed of the stirrer 75 min^{-1}. 600 ml of artificial intestinal juice, pH 6.8 were used as release medium. The released quantity of active ingredient present in the dissolution medium at each point in time was determined by spectrophotometry.

Time	Amount released
60 min	33%
240 min	76%
480 min	100%
720 min	108%

EXAMPLE 4

Components	Per tablet	Per batch	%
Tramadol	116.5 mg	349.0 g	34.9
Polyethylene oxide 7 000 000 (Polyox WSR 303, DOW Chemicals)	150.2 mg	450.0 g	45.0
Polyethylene glycol (PEG 6000)	33.4 mg	100.0 g	10.0
Hypromellose (Metholose 90 SH 100 000 cP, ShinEtsu)	33.4 mg	100.0 g	10.0
Butylhydroxytoluene	0.3 mg	1.0 g	0.1
	333.8 mg	1000 g	100%

45 g of the polyethylene oxide and 1 g butylhydroxytoluene were mixed to a homogeneous mixture by means of a mortar. All the further components were added and mixed for 15 minutes in a free-fall mixer.

Extrusion was performed using a model Micro 27 PH 40 D twin screw extruder manufactured by Leistritz (Nürnberg). Screws having eccentric ends were used. The die used is a heatable round die having a diameter of 9 mm.

The following parameters were selected for extrusion:

Screw speed:	100 rpm
Throughput:	4 kg/h
Product temperature:	134° C.
Casing temperature:	heating zones 1 to 10: 100° C. heating zone 11 (die): 120° C.

The extrudate, which was still hot, was cooled. No nitrogen atmosphere was used. The product did not exhibit any yellowish discoloration.

The cooled strand was singulated into biplanar slices. The final press-forming was performed by means on an eccentric tablet press (model EK0). Round punches (diameter 10 mm) having a radius of curvature of 8 mm were used as tabletting tool. One tablet was obtained from one slice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to a force of 500 N. The tablet could not be comminuted with a hammer. This could not be achieved with the assistance of a pestle and mortar either.

EXAMPLE 5

Components	PerTablet	Per batch	%
Oxycodon HCl	40.00 mg	133.3 g	13.3
Polyethylene oxide 5 000 000 (Polyox WSR Coagulant, DOW Chemicals)	190.0 mg	643.3 g	63.3

-continued

Components	PerTablet	Per batch	%
Polyethylene glycol (PEG 6000)	30.0 mg	100.0 g	10.0
Hypromellose (Metholose 90 SH 100 000 cP, ShinEtsu)	30.0 mg	100.0 g	10.0
α-Tocopherol	5.0 mg	16.7 g	1.7
Aerosil (highly disperse SiO_2)	5.0 mg	16.7 g	1.7
	300 mg	1000 g	100

50 g of the polyethylene oxide, 5 g α-tocopherol and 5 g Aerosil were mixed to a homogeneous mixture by means of a mortar. All the further components were added and mixed for 15 minutes in a free-fall mixer.

Extrusion was performed using a model Micro 27 PH 40 D twin screw extruder manufactured by Leistritz (Nürnberg). Screws having eccentric ends were used. The die used is a heatable round die having a diameter of 9 mm.

The following parameters were selected for extrusion:

Screw speed:	100 rpm
Throughput:	4 kg/h
Product temperature:	134° C.
Casing temperature:	heating zones 1 to 10: 100° C. heating zone 11 (die): 120° C.

The extrudate, which was still hot, was cooled. No nitrogen atmosphere was used. The product exhibited a slight yellowish coloration. However, this coloration was merely caused by the natural color of α-tocopherol, but was not intensified by the extrusion, i.e. the extrusion was performed without discoloration.

The cooled strand was singulated into biplanar slices. The final press-forming was performed by means on an eccentric tablet press (model EK0). Round punches (diameter 10 mm) having a radius of curvature of 8 mm were used as tabletting tool. One tablet was obtained from one slice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to a force of 500 N. The tablet could not be comminuted with a hammer. This could not be achieved with the assistance of a pestle and mortar either.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur. The temperature of the release medium was 37° C. and the rotational speed of the stirrer 75 min^{-1}. 600 ml of artificial intestinal juice, pH 6.8 were used as release medium. The released quantity of active ingredient present in the dissolution medium at each point in time was determined by spectrophotometry.

Time	Amount released
60 min	33%
240 min	76%
480 min	100%
720 min	108%

The invention claimed is:

1. An abuse-proofed dosage form thermoformed by extrusion without discoloration comprising one or more active ingredients with abuse potential (A), optionally physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein the dosage form exhibits a breaking strength of at least 500 N, the one or more active ingredients with abuse potential (A) are selected from the group consisting of oxymorphone and physiologically acceptable compounds and derivatives thereof, and the polymer (C) comprises polyethylene oxide having a molecular weight of at least 0.5 million g/mol.

2. The dosage form according to claim 1, which is in the form of a tablet.

3. The dosage form according to claim 1, wherein the molecular weight of the polyethylene oxide (C) is at least 1 million g/mol.

4. The dosage form according to claim 3, wherein the molecular weight of the polyethylene oxide is in the range of from about 1 to about 15 million g/mol.

5. The dosage form according to claim 1, which comprises the wax (D), and the wax (D) is at least one natural, semi-synthetic or synthetic wax with a softening point of at least 60° C.

6. The dosage form according to claim 5, wherein the wax (D) is carnauba wax or beeswax.

7. The dosage form according to claim 1, which additionally comprises:

(a) at least one substance which irritates the nasal passages and/or pharynx; and/or

(b) at least one viscosity-increasing agent, which in the presence of an active ingredient extracted from the dosage form using a liquid medium, forms a gel with the extract obtained from the dosage form, which gel optionally remains visually distinguishable when introduced into a further quantity of an aqueous liquid; and/or

(c) at least one antagonist for the active ingredient or active ingredients with abuse potential; and/or

(d) at least one emetic; and/or

(e) at least one dye; and/or

(f) at least one bitter substance.

8. The dosage form according to claim 7, wherein component (b) is at least one viscosity-increasing agent selected from the group consisting of microcrystalline cellulose combined with carboxymethylcellulose sodium, polyacrylic acid, locust bean flour, pectins, waxy maize starch, sodium alginate, guar flour, iota carrageenan, karaya gum, gellan gum, galactomannan, tara bean flour, propylene glycol alginate, apple pectin, sodium hyaluronate, tragacanth, tara gum, fermented polysaccharide welan gum, and xanthan gum.

9. The dosage form according to claim 1, which comprises at least one active ingredient with abuse potential (A) at least partially in controlled release form.

10. The dosage form according to claim 9, wherein each of the active ingredients with abuse potential (A) is present in a controlled release matrix.

11. The dosage form according to claim 10, wherein the controlled release matrix material comprises component (C) and/or the optionally present component (D).

12. The dosage form according to claim 1, which comprises a core and a tubular domain surrounding the core, wherein said tubular domain has a morphology different from that of the core.

13. The dosage form according to claim 12, wherein the core and the tubular domain have substantially the same chemical composition.

14. The dosage form according to claim 12, wherein the tubular domain does not completely cover the core.

15. The dosage form according to claim 1, which comprises a physiologically acceptable auxiliary substance (B), and the physiologically acceptable auxiliary substance (B) is an antioxidant.

16. The dosage form according to claim 15, wherein the antioxidant is selected from the group consisting of ascorbic acid, salts of ascorbic acid, butylhydroxyanisole, butylhydroxytoluene, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, sodium bisulfite and α-tocopherol.

17. A process for the production of a dosage form according to claim 1, comprising:

I) mixing components (A), the optionally present component (B), (C) and the optionally present component (D);

II) heating the resultant mixture in the extruder at least up to the softening point of component (C) and extruding the mixture as extrudate through the outlet orifice of the extruder by application of force; and

III) singulating and forming the still plastic extrudate into the dosage form; or

IV) cooling and forming the optionally reheated singulated extrudate into the dosage form.

18. The process according to claim 17, wherein process step II) is performed by means of a twin-screw-extruder.

19. The process according to claim 17, wherein process steps II) and III) and optionally process steps I) and IV) are performed under an inert gas atmosphere.

20. The process according to claim 19, wherein nitrogen is used as the inert gas atmosphere.

21. The process according to claim 17, wherein mixing of the components according to process step I) proceeds in the extruder under an inert gas atmosphere.

22. The process according to claim 17, wherein the mixture according to process step I) is extruded through a die with at least one bore.

23. The process according to claim 17, wherein the extrudate is singulated by cutting.

24. The process according to claim 17, wherein the extrudate is in the form of a strand and is shaped and singulated with the assistance of counter rotating calender rolls comprising opposing recesses in their outer sleeve.

25. The process according to claim 17, wherein the singulated extrudate is pelletized or pressed into tablets.

26. The process according to claim 17, wherein swelling and expansion of the dosage form upon storage is suppressed by press forming the singulated extrudate at a pressure of at least 1 kN and a temperature of between 25° C. and 40° C. below the melting range of the mixture of the components.

27. A dosage form according to claim 1, wherein the physiologically acceptable compounds and derivatives are salts, solvates, esters, ethers and amides.

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